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MEDICAL ANNALS of the DISTRICT OF COLUMBIA

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VENEREAL DISEASE NUMBER

July 1966 Vol. XXXV · No. 7

PHS Venereal Disease Program
William J. Brown, M.D.

Chain of Venereal Disease Control
C. Wendell Freeman, M.D.

Laboratory Diagnosis of Venereal Disease
G. W. H. Schepers, M.D., D.Sc.

Diagnosis of Early Syphilis
Sidney Olansky, M.D., F.A.C.P.

Diagnosis and Management of Gonorrhea
Aston B. Greaves, M.D.

Treatment of Syphilis and Gonorrhea
Eugene J. Gillespie, M.D.

Venereal Disease Research
James B. Lucas, M.D.

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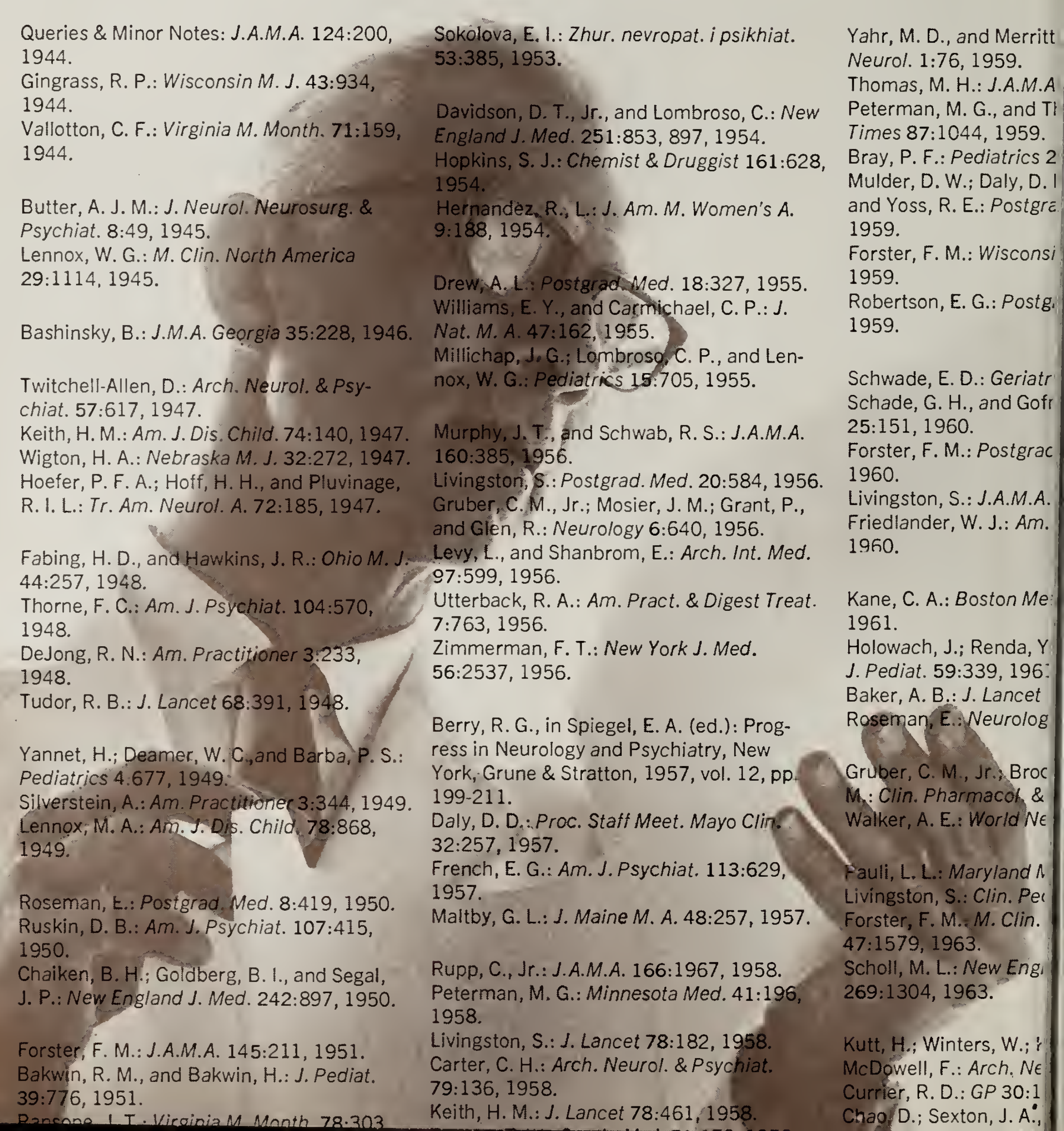

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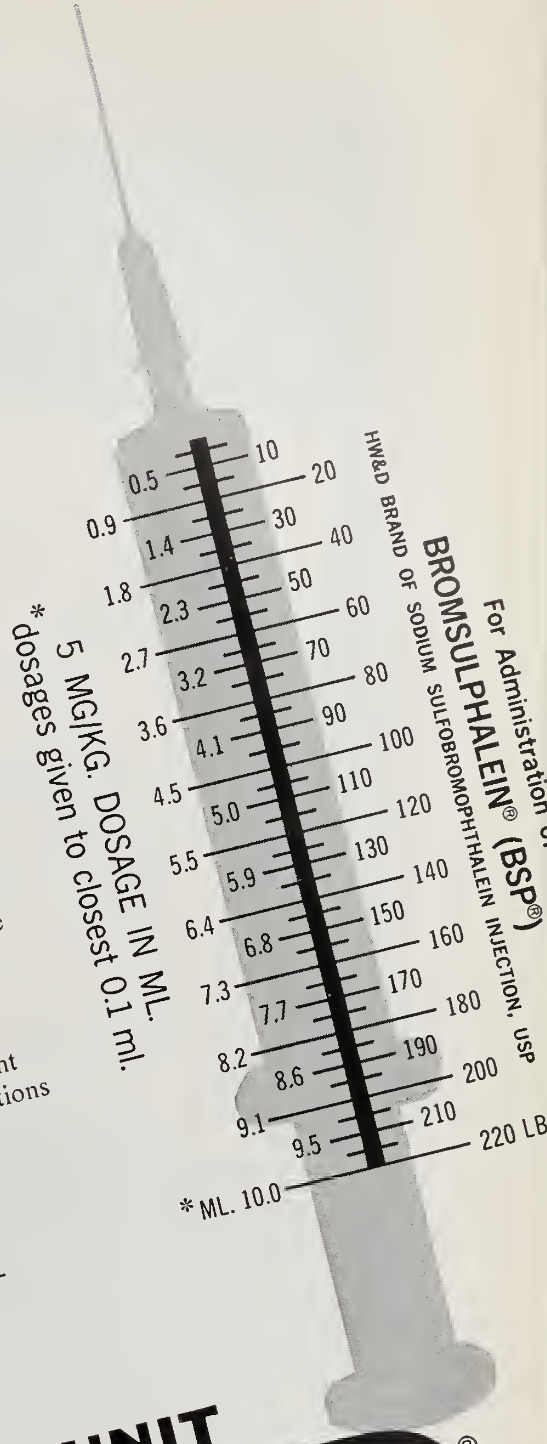
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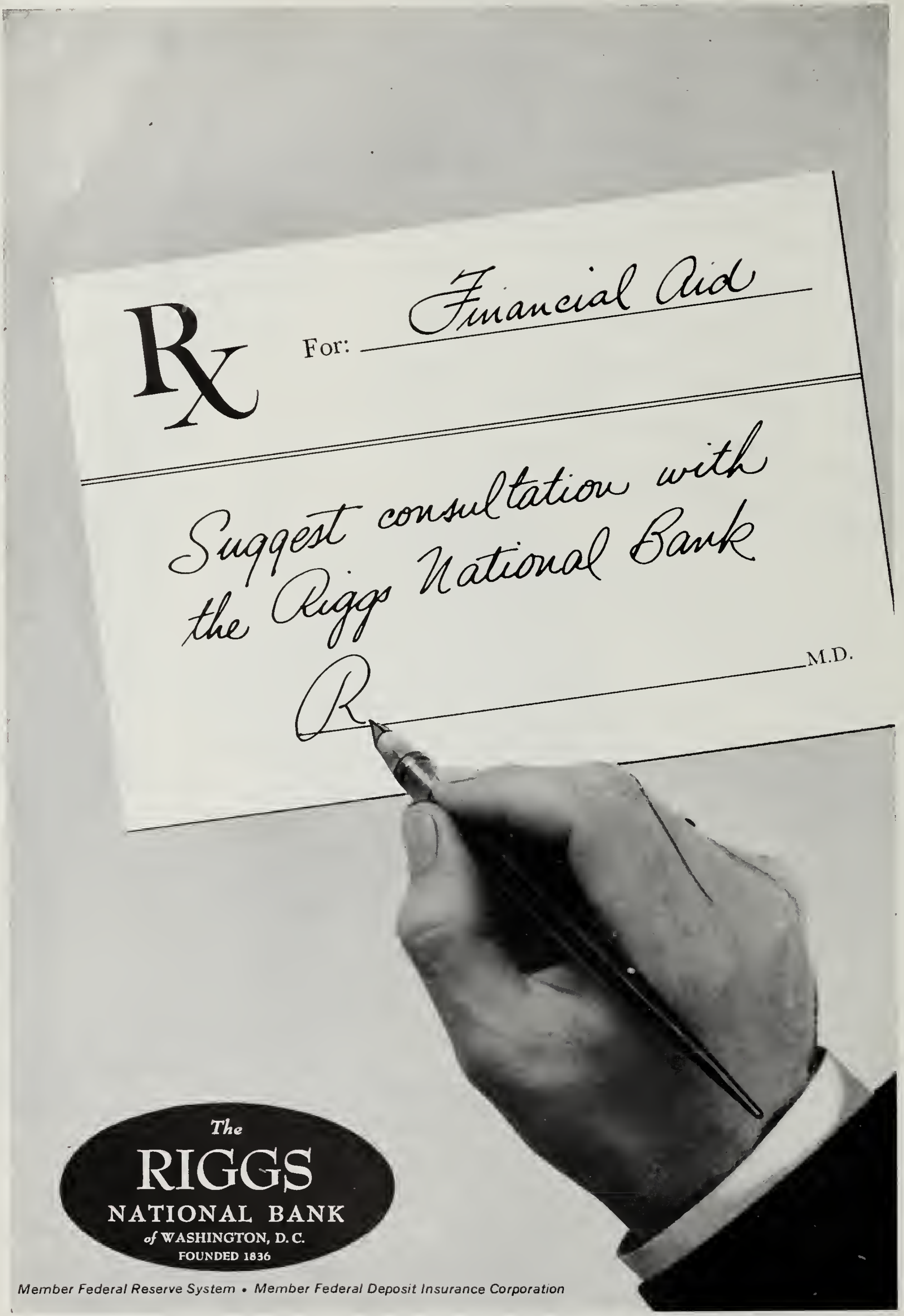
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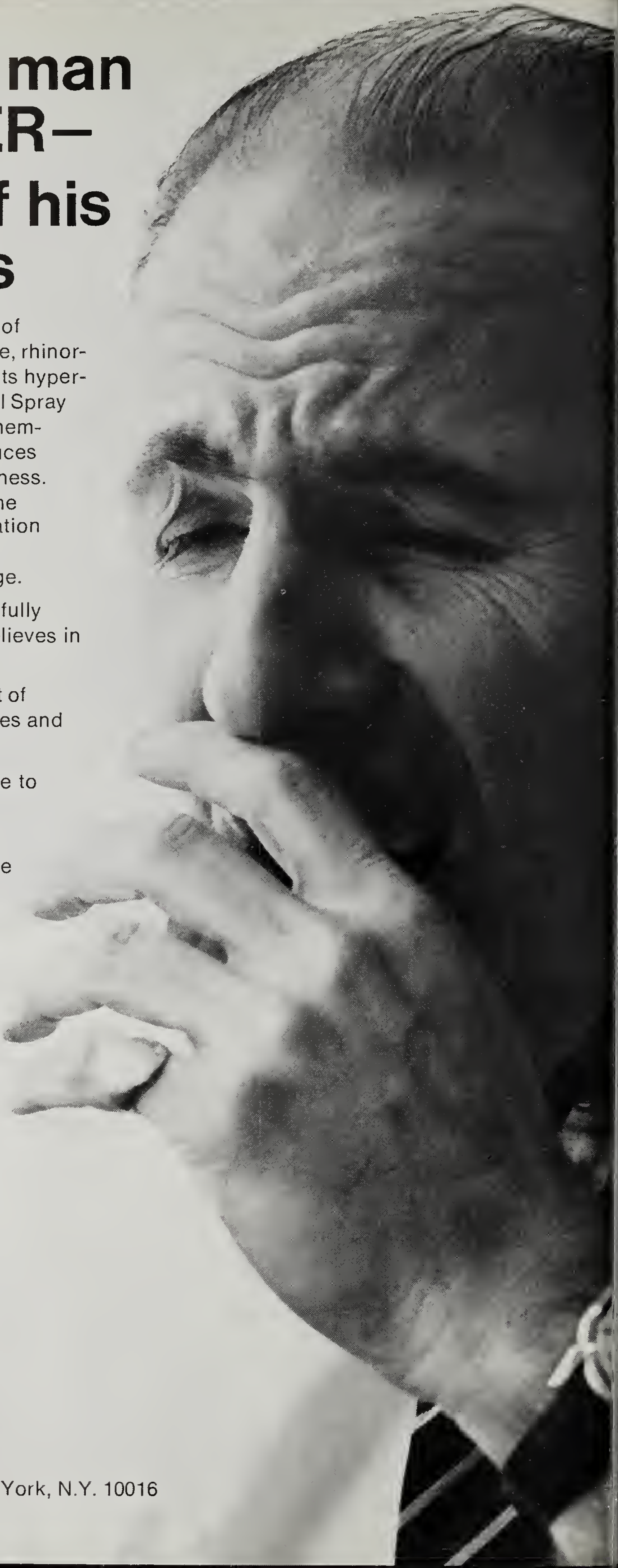

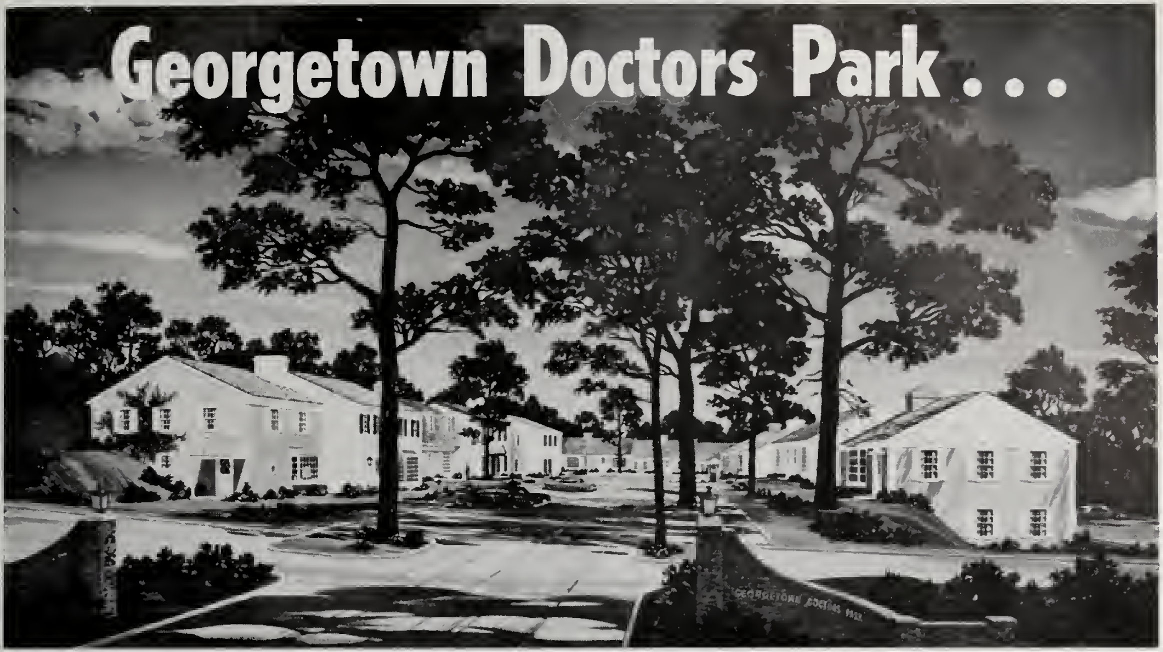

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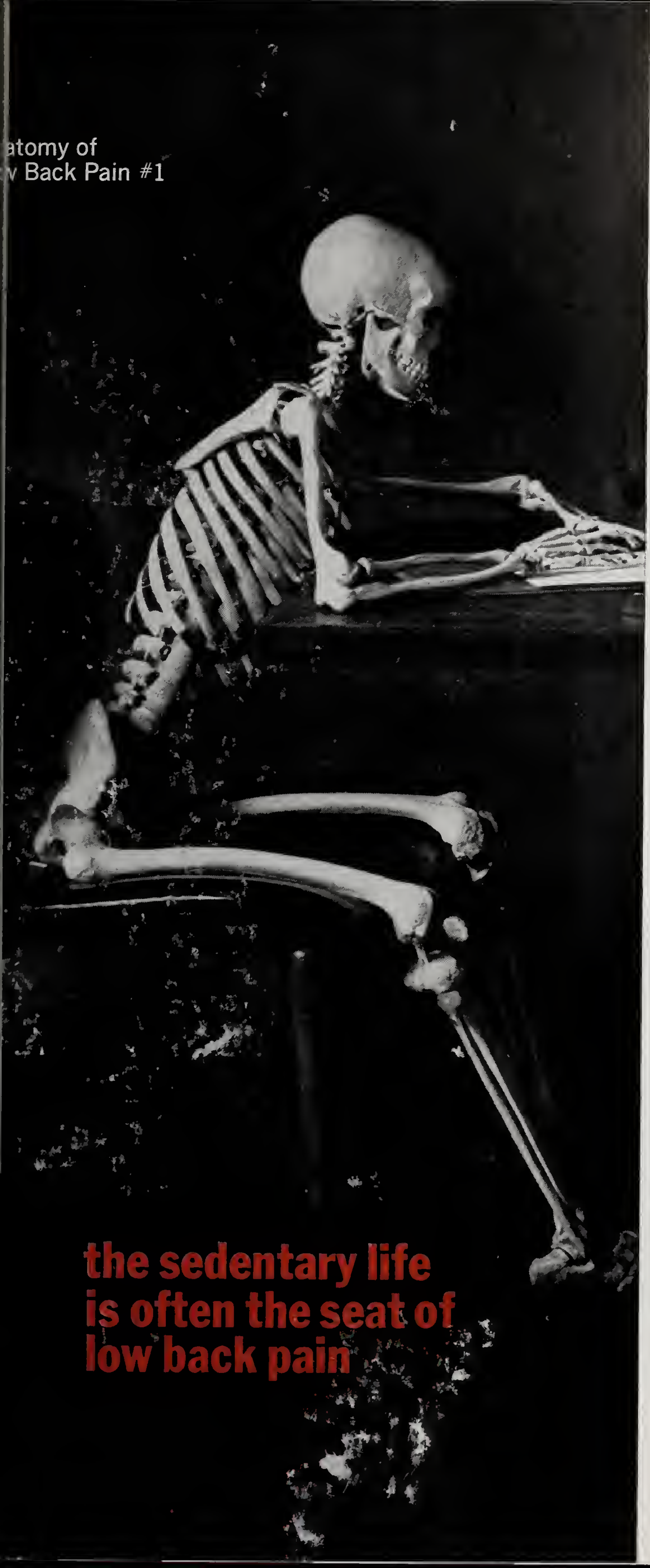

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Side Effects: The only side effect reported with any frequency is sleepiness, usually on higher than recommended doses. An occasional patient may not tolerate carisoprodol because of an individual reaction, such as a sensation of weakness. Other rarely observed reactions have included dizziness, ataxia, tremor, agitation, irritability, headache, increase in eosinophil count, flushing of face, and gastrointestinal symptoms.

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Shalowitz, M.: Int. Rec. Med. 174:357, June, 1961.

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Vistaril (hydroxyzine) was evaluated for relief of postalcoholic syndrome in 52 chronic alcoholic outpatients over a period of two to four weeks. Many patients received partial to complete relief of psychomotor agitation, anxiety, irritability, craving, insomnia, depression, anorexia, nausea and tension. "*No evidence of toxicity or habituation was noted.*" "*No difficulty was experienced in discontinuing medication.*"

Greenhouse, H. R.: Med. Times 91:1069, November, 1963.

Of 326 alcoholics treated with hydroxyzine for the postalcoholic syndrome, satisfactory control was achieved in 276 (85%). "*As is not the case with other tranquilizers, hydroxyzine has no published record of causing addiction and dependence or withdrawal symptoms.*" Goldman, H. I.: Southwest. Med. 42:276, June, 1961.

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Lapolla, A.: Clin. Med. 8:1332, July, 1961.

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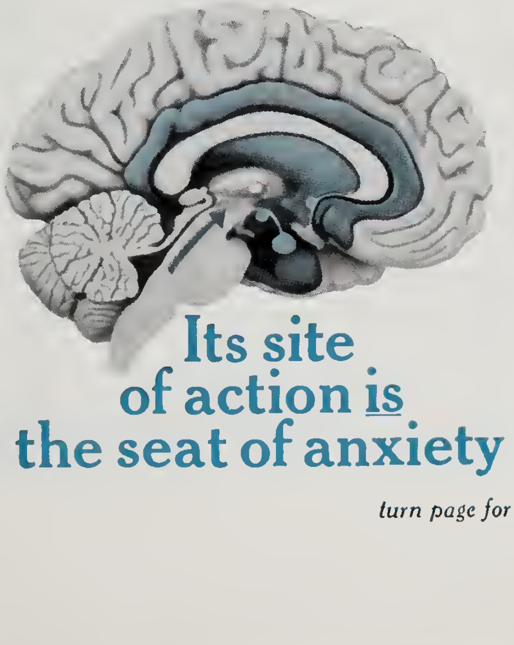

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BRIEF SUMMARY

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Precautions: Hydroxyzine may potentiate the action of central nervous system depressants. In conjunctive use, dosage for these drugs should be decreased, as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. On reported intravenous injection a few instances of digital gangrene have occurred distal to the injection site, considered to be due to inadvertent intra-arterial injection or possibly periarterial extravasation. Therefore, particular caution should be observed to insure injection only into intact veins; avoid either intra-arterial injection or extravasation. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose.

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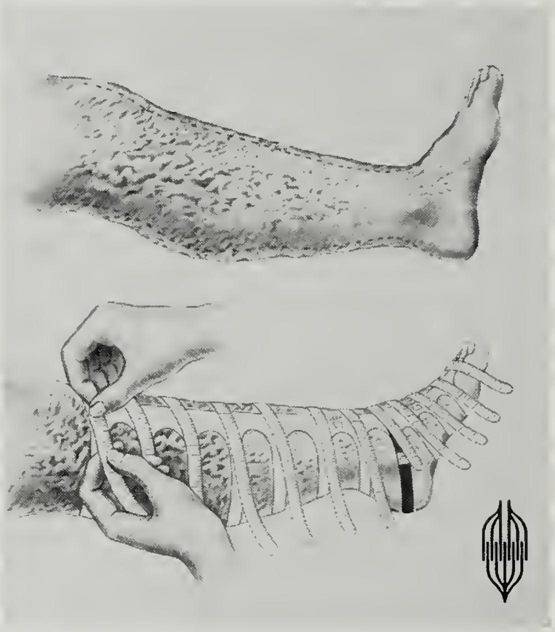

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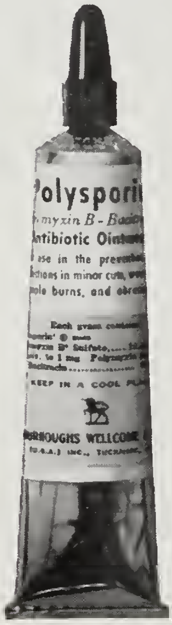

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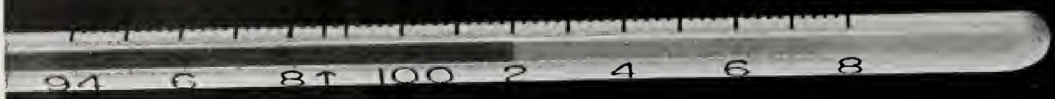

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MEDICAL ANNALS

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July 1966 VOLUME XXXV • NUMBER 7

An Introductory Note on the Venereal Disease Seminar

THE VENEREAL DISEASE SEMINAR was held in Washington, D. C., March 2 and 3, 1966, at the new headquarters of the Medical Society of the District of Columbia. The Seminar was presented by the District of Columbia Department of Public Health; it was co-sponsored by the Medical Society of the District of Columbia, the Medico-Chirurgical Society of the District of Columbia, Inc., and the Social Hygiene Society of Metropolitan Washington.

The purpose of the Seminar was to serve as a refresher course for private physicians in the recognition and treatment of venereal diseases.

The Program Committee, which was responsible for securing the excellent speakers, consisted of Dr. John A. Kenney, Chairman; Dr. Paul B. Cornely, Dr. James A. Curtin, Dr. C. Wendell Freeman, and Mr. Philip Donahue, epidemiologist.

Dr. Freeman, representing the D. C. Health Department, headed the Steering Committee which had overall responsibility for planning the 2-day meeting. Assisting him were Dr. Kenney, of the Medico-Chirurgical Society of D. C.; Mr. Robert H. Conn, also of the D. C. Health Department; Mr. Fred Trust, D. C. Medical Society; Mr. William Benedict, Social Hygiene Society; and Mrs. Lucile Tibbs, of the D. C. Health Department, who served as registrar.

The papers delivered at the Seminar and published in this issue of the MEDICAL ANNALS present the latest information available on the diagnosis, management and control of syphilis and gonorrhea.

The Public Health Service Venereal Disease Program*

WILLIAM J. BROWN, M.D.†

AT THE PRESENT TIME the Federal budget for venereal disease amounts to approximately 10 million dollars. Most of this money is allocated to State or large-city Health Departments under a "project grant" system which fundamentally distributes funds between States on the basis of the syphilis problem, availability of State or local funds, and willingness to attack the problem. In addition to project grants to States a certain portion of the funds appropriated by Congress each year is allocated to research, training, and to Central Office administration.

The Public Health Service acts in an advisory capacity only in its relation to State programs. We attempt to provide leadership, but we can only make suggestions as to the program content.

In addition to granting funds, we assign case-finding personnel in lieu of funds. The administration of our project grant program with States and the evaluation of results of expenditures of funds in terms of attainment of program goals are 2 major functions of our headquarters office in Atlanta. Research studies and training in venereal disease work are also directed from our headquarters office. I shall not attempt to list all of the functions of our Central Office, but I might mention that we maintain liaison with other governmental agencies, such as the Military, Foreign Quarantine, Indian Health, and Veterans Administration Hospitals. Our office works very closely with the American Social Health Association, the American Medical Association, the American Hospital Association, the American Venereal Disease Association, Red Cross Blood Banks, the World Health Organization, and other national and international health agencies.

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* Presented at the National Symposium on Venereal Disease Control which was sponsored by the American Medical Association in Chicago, Illinois, November 20, 1965.

† Chief, Venereal Disease Branch, Communicable Disease Center, Public Health Service, United States Department of Health, Education, and Welfare, Atlanta, Georgia 30333.

The national venereal disease control program in this country was launched back in 1939. In 1961 the Surgeon General of the Public Health Service established a Task Force on Syphilis Control and Eradication. The need for such a committee was painfully evident when one considers that reported cases of infectious syphilis were rising year by year at an alarming rate. The Surgeon General, urged by concerned members of Congress, charged the Task Force Committee with the responsibility for reviewing the syphilis problem and the control programs designed to combat it, and to recommend a course of action which would lead to the eradication of syphilis as a public health problem within a reasonable period of time.

This committee, chaired by Dr. Leona Baumgartner, then Commissioner of Health in New York City, carefully appraised the problem and the tools to cope with it, and thus developed their now well-known report. They reasoned that a disease whose cause was known and which is relatively easy to diagnose and even easier to treat certainly could be controlled and eliminated within the foreseeable future if a well-conceived, balanced, and dynamic program were launched and carried out throughout the Nation, notwithstanding the fact that a vaccine was not available.

The primary recommendation of the Task Force was that an intensive effort be inaugurated to enlist the private physician and his professional societies and associations in the control effort, providing for at least 2 visits per year by a qualified health worker to 100,000 general practitioners in the country and 1 visit a year to the remaining 130,000 physicians. The purpose of the visit is to alert the physician to the increasing syphilis problem, to raise his index of suspicion in differential diagnosis, to encourage him to report all of his syphilis cases, and to have him consider an infectious case of syphilis as a public health emergency which requires immediate epidemiologic follow-up. Each visit includes a discussion with the doctor of the need for a trained Health Department interviewer to interview every infectious syphilis patient and every early latent syphilis patient under private care. It is made clear, however, that such confidential interviews are never performed without the prior permission of the physician concerned.

Another major recommendation of the Task Force Committee was that intensive follow-through be applied in all cases of infectious and early latent syphilis. Briefly, the concept of syphilis eradication depends on finding cases of infectious syphilis as quickly as possible and applying early and intensive syphilis epidemiology in every case to locate the source and spread of cases. By infectious syphilis I mean the primary or secondary stage of the disease. By early latent syphilis I mean syphilis of less than 4 years' duration. We are conducting a study to examine carefully the epidemiologic yield of early latent syphilis, and the definition may well change to syphilis of less than 2 years' duration. Syphilis epidemiology consists of interviewing every infectious and early latent syphilis patient to obtain the names of all sex contacts, followed by rapid location and examination of all exposed contacts. In addition to treatment of patients with syphilis, "epidemiologic treatment," also called "preventive" or "prophylactic" treatment, is recommended to be administered to all sex contacts who are clinically and serologically negative on initial examination. Every case of infectious and early latent syphilis reported by a private physician or clinic triggers action by the Health Department. Each case report serves as a basis for starting the whole epidemiologic process, since the source of infection and the exposed contacts are potential starts of another outbreak or epidemic.

Patient-interviewing and contact-tracing are performed by professional personnel. We expend much effort and money each year training young college graduates in methods of professional interviewing. Doctor-patient relationships are always considered and maintained. All information concerning diagnosis and admitted sex relations between patients and contacts is always held in the strictest confidence.

Although the physician is responsible for seeing to it that follow-up case-finding is applied in all infectious and early latent syphilis patients under his care—and the recent survey conducted by the American Social Health Association and the American Medical Association showed that private physicians diagnose and treat 80 per cent of all infectious syphilis patients treated in this country—he cannot perform this follow-through himself for 2 reasons. In the first place, interviewing patients for sex contacts is time-consuming, and the average physician is too busy to devote up to an hour interviewing each patient. In the second place, the contacts named by the patient often live in another city or state. This is why the Public Health Department, acting as an agent of the physician, performs the patient-interviewing and contact-tracing. Only when the private physician does his part by reporting each patient and allowing a trained Health Department representative to interview his patient for sex contacts can we hope to control and eradicate syphilis.

In the 3 years since implementation of the Task Force recommendation concerning physician visitation we have not reached our goal of visiting every single physician. But last year Health Department representatives visited more than 90,000 private doctors, and during the past 3 years a majority of the physicians in private practice in the United States were visited personally by professional health workers. Thus one can see from the very volume of this visitation activity how serious we are to enlist the coöperation and active participation of every doctor in the United States.

Over and above syphilis case-finding, the Task Force realized the vast potential opportunity presented by routine blood-testing. This control aid would provide syphilis intelligence the means to find additional cases outside of known contacts. Thus, the added infectious syphilis cases found through blood-testing will serve as "starters" for discovering more cases.

Blood-testing, both voluntary and required, is a major syphilis case-finding method. The Public Health Service has always recommended maintenance of such control devices as routine blood-testing procedures on all adults admitted to a hospital, premarital partners, prenatal women, premilitary inductees, and pre-employment persons. Certainly, in a period of high syphilis incidence our policy is to strongly support such screening programs.

Blood-testing programs provide an index to syphilis prevalence and find a considerable number of cases of syphilis in the latent stage. Treatment instituted at this point prevents late disabling effects of the disease and reduces the occurrence of congenital syphilis. Such programs also find many cases of infectious syphilis and thus provide "starter" cases to which subsequent contacts may be found and from which other cases and new chains emanate.

In the past it has been determined that many specimens of blood examined in hospitals on routine admissions were reactive (or positive) but that the laboratory slip was filed in the patient's chart and forgotten. Also, there is the rather large problem of persons with reactive test results who receive adequate diagnostic and treatment services but who are not reported to the Health Department. In order to plug such holes in our syphilis intelligence system the Public Health Service is recommending and supporting state legislation which requires that all laboratories notify Health Departments of all reactive blood tests for syphilis. This does not constitute a case report of syphilis or a morbidity report as we in Public Health work know it, but it merely alerts the Health Department that a case of syphilis may exist in the community and that Health Department surveillance should be maintained to insure that every reactive report is finally followed through to a medical diagnosis of syphilis or not syphilis, that an appropriate report be made to the Health Department, and that a good epidemiologic survey be applied when indicated. Incidentally, the serologic reactor notification program brings to Health Departments' attention approximately 30 per cent of infectious syphilis cases reported per year. And, of course, case-finding is immediately applied in each case so detected to uncover the source of infection as well as any "spread" cases.

There has been some resistance to such reactor notification by certain medical groups and some laboratory directors, but I am happy to report to you that, whereas 11 States had such regulations in 1961, there are now 28 such States. I must add, however, that even with a State regulation concerning reactor notification, some laboratories fail to report reactive specimens to the Health Department and that other laboratories report only partially.

About 35 million specimens of blood are drawn for syphilis tests each year in the United States, and approximately 1,200,000 of such specimens are positive. Our follow-up procedure has about 50 per cent of these under surveillance. This means that the dispositions of about 600,000 reactive specimens are unknown to the Health Department. It is estimated that 7,300 cases of primary and secondary syphilis are lost to Health Department surveillance because of this gap in our syphilis intelligence.

In the area of routine blood tests we are currently trying to reinstate routine serologic testing for syphilis of all adult patients admitted to hospitals throughout the country. A recent survey done in coöperation with the American Hospital Association showed that 3.1 per cent of approximately 17 million serologic specimens tested in hospitals annually were reactive for syphilis. We recently had some discussion with the Joint Commission on Accreditation of Hospitals, but our proposal for reinstatement has not been accepted. However, the door was left open and we hope to reintroduce the suggestion and would greatly appreciate the active support of the American Medical Association.

The Task Force also recommended that an aggressive, dynamic program of professional and public education be launched as an integral part of the new program. Education for the lay public was designed to encourage persons to volunteer for examination and treatment if they recognized or suspected a sign or symptom of syphilis, or if they were exposed to the disease. I am very pleased to see that the American Medical Association has also started a vigorous venereal disease educational campaign. But education alone cannot control and certainly cannot eradicate syphilis. Intensive case-finding search provided by Public Health and prophylactic treatment of all sex contacts must be a part of the program if it is to succeed. Without these 2 components of control we cannot do the job.

In addition to mass media an intensive educational program has been directed toward adolescents in both elementary and high schools to inform young persons of the hazards of venereal disease. As one might imagine, this phase of our education program has met with resistance on the part of some parents and school administrators. However, in spite of these obstacles we have made progress in this area.

In addition to public educational efforts we have worked with medical schools in an effort to reinstate or expand the teaching of the medical aspects of syphilis. We also provide nationally known experts to speak to State and County Medical Societies about the management of syphilis. We are striving to raise physicians' index of suspicion toward syphilis through private seminars and articles in medical journals.

As a further aid to teaching management of venereal disease, in several areas venereal disease patients are sent to hospitals, with specially assigned teaching fellows, so that medical students, as well as house physicians, can work with "live" syphilis patients. In other areas medical students receive training in the venereal diseases in local venereal disease clinics.

In line with further recommendations of the Task Force our scientists at the Venereal Disease Research Laboratory in Atlanta are attempting to develop a vaccine for syphilis. They are also trying to perfect a single standard serologic test for syphilis that will replace the several types of blood tests now being done.

In addition, our bench scientists are quietly working to develop a good, inexpensive, and relatively simple diagnostic test for detecting gonorrhea in the female. Until this is accomplished and we are sure of the effective penicillin dosage level in females with gonorrhea, I do not believe a gonorrhea control program can be effective. That is why my remarks have been largely confined to our syphilis program.

I have tried to outline for you the Public Health Service's role and interest in venereal disease control in this country. I hope I have succeeded in getting across the main elements of the national syphilis eradication program and our relationship to State and County Health Departments, but, most of all, I have tried to point out the part every physician in the Nation should play in this program.

Look for syphilis. Report syphilis when you find it. Demand that competent Health Department epidemiologists interview your patients with syphilis, especially infectious syphilis. Insist that the source case be found, as well as any "spread" cases involved in the chain of infection. Give preventive or epidemiologic treatment to negative sex contacts. And participate with your Health Departments in all aspects of the syphilis program.

I know that the American way of doing things will prevail in this matter of syphilis control and eradication and that the Public Health Service and State and local Health Departments can depend on the American private practitioner to meet this challenge forthrightly and get on with the business of eradicating this disease from our people once and for all.

The Chain of Venereal Disease Control

C. WENDELL FREEMAN, M.D.*

A CHAIN IS NO STRONGER than its weakest link. Each link comprising the chain of venereal disease control must be forged into an effective component if the total control effort is to be effective.

The first link in the chain is case-finding. Without this, no program can be effective. The ideal case-finding program would envision every individual with venereal disease being brought to examination, diagnosis and treatment. Each infected patient would be interviewed by trained epidemiologists to determine the source and spread of the infection. Having tactfully and confidentially secured this information, we spare no effort to make certain that these persons are brought in for examination and treatment if indicated. Perhaps the exposed patient may be willing to be treated prophylactically to prevent any possible symptoms of the disease. The contacts must be questioned as to their contacts until every possible infected person has been examined.

Each private physician, so important in the eradication program, must be urged to coöperate by reporting his VD patients to the Health Department and, more importantly, permitting such patients to talk with the epidemiologists. The private physician plays the most important role. Surveys indicate that 75 to 80 per cent of all venereal diseases are now treated in private physicians' offices. He is the key to case-finding and control. If patients and their physicians could face the fact that a venereal disease is an infectious disease, unfortunate to be sure, but not a disgrace, our path of control would become easier. Private physicians are visited regularly by Public Health personnel. These visits are made to keep the private physician informed about the latest developments in the venereal disease field; to acquaint him with the many services available to him by the Health Department; and, finally, to urge his coöperation in the epidemiological process. There may be a new diagnostic test or a new or improved therapeutic agent which has just been approved but which has not yet reached the literature; perhaps there is need for diagnostic or consultative services. We hope he will give permission for interview and contact investigation of all syphilis patients seen by him.

No case-finding program can be stronger than the capabilities of its epidemiological section. It is this group who must interview the infected patient for their sexual contacts, seeking source and possible spread of an infection. Case-finding by physician visitation, by laboratory surveillance, and by surveys are all important in the search for new infections.

The second link in the chain is clinical facilities for the optimum care of the patient. In venereal disease control, coöperation of the patient is absolutely essential. The thoughtful, sympathetic, kindly attitude toward the patient seeking medical help will pay handsomely when interviewers attempt to elicit contacts. If the patient feels that from the moment he steps through the door to the time he reaches the epidemiologist he has been treated with consideration and understanding, his desire to coöperate in treatment and investigation can the more readily be assured. If verbal abuse and condescension have been his lot, no coaxing or threats will win his coöperation. Calling a patient Mr. or Mrs. instead of John or Mary, giving a smile rather than a scowl or a kind word instead of an accusing finger will get results not possible in any other way. The clinic should be as bright and as cheerful as it is possible to make it. The patient must be made to feel that he is the most important part of this setup. Loud talking or arguments, or boisterous groups in halls will not contribute to confidence or coöperation on the part of the patient.

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The clinics should be staffed with physicians, epidemiologists, Public Health nurses, registered nurses, nursing aides, and clerks, each of whom is aware of the importance of his contribution to the success of the combined effort. A kind word from a registering clerk may be most important in determining the attitudes and the extent of the patient's coöperation. The medical staff must be well trained in the clinical diagnosis of venereal diseases and be able to perform the diagnostic tests and to use the most effective therapeutic measures required in venereal disease management. He should recognize that in any active treatment program some reactions will occur. He should be able to recognize these reactions and take immediate remedial measures to combat these unfavorable responses.

The third link in the chain of venereal disease control is education. There is a woeful lack of understanding of venereal disease in children from eighth grade through junior and senior high schools. Surveys have indicated that the majority of these students do not know how these diseases are contracted or have any basic knowledge of the symptoms. Venereal disease and sex education must be a part of the educational program in health education in the public schools. This education should be given by the health teachers with the Health Department supplying refresher courses for such teaching groups. Moving pictures, pamphlets, placards, leaflets and similar educational materials appropriate for these young people should be available for use in the classrooms.

Every adult should know the facts of venereal disease—facts of symptoms, of prevention, of availability of treatment facilities. Speakers to impart this information must be readily available to parent-teachers associations, to church groups, to civic associations, and to similar lay audiences. The entire community should be organized systematically so that there will be no adult who has not heard the story and learned the facts. Syphilis and gonorrhea must be discussed as infectious diseases calmly and impersonally. The relation of venereal disease to sex conduct is only incidental. Misconceptions, prudery and guilt complexes must be replaced by frank discussions of symptoms, prevention and cure.

Education and information must be provided for the medical profession. Many of the younger physicians have had no contact with infectious syphilis. Refresher courses and assignment of Health Department physicians to hospitals and medical schools can make certain that the medical student and the young physicians will be aware of the lesions and symptoms of venereal diseases. Through physician visitation the practicing physician is encouraged to remain alert to the possibility that these patients will come to his office. He is urged to be vigilant and, through awareness, maintain suspiciousness of mind. He is informed how the program works to eliminate syphilis and of his essential role in the control program by reporting cases and allowing interviews.

The fourth link in the chain of venereal disease control is services by the local Health Department. Medical consultation on venereal diseases, serologic, dark-field and other tests, spinal fluid examination, field epidemiology, and treatment are all free services available to practicing physicians. It is hoped that, having availed himself of these services, the physician will more readily permit his patients to be interviewed. Only a fraction of the patients infected with venereal diseases are being reported and have epidemiological study.

The final link in the chain of veneral disease control is the legal link. The communicable disease law requires that every case of venereal disease be reported to the Health Department. Unfortunately, this law is practically unenforceable. Private physicians are hampered by the insistence of private patients that their case not be reported. The association of venereal diseases with sexual activity makes patients insist that their private physician not report their case for investigation. The possibility of embarrassment, exposure of clandestine relations, fear of loss of position or employment, and many other reasons are given to explain why the infected patient insists on not being reported. It requires a dedicated and coöperative physician to insist on reporting such patients in spite of their objections. If both the patient and the physician would realize that the epidemiological investigations are entirely confidential and free of embarrassment, greater participation could be expected. It should be stressed that bringing the infected partner to diagnosis and treatment might very well prevent blindness, insanity, heart disease, or death in that patient. When syphilis or gonorrhea become known as mere infectious diseases and not punishment for sin, we will have progressed a long way toward control.

(*Continued on page 374*)

Laboratory Diagnosis of Venereal Disease*

G. W. H. SCHEPERS, M.D., D.SC.†

THE OVERT SIGNS of all the venereal diseases are quite transient while their serious sequelae and complications often develop insidiously. To a significant extent, therefore, diagnosis depends on data obtained through complicated technological procedures.

When Neisser first identified the gonococcus and after the *Treponema pallidum* was recognized as the cause of syphilis, microscopic recognition of gonorrhea and syphilis seemed greatly simplified. The principle of laboratory diagnosis still depends on proving the existence of these etiologic agents or on demonstrating results of their interaction with the human host. However, the technologic task now is quite elaborate. The laboratory problem has been complicated because patients often coöperate poorly yielding unsatisfactory specimens and these diseases have acquired epidemic prevalence so that large numbers of specimens have to be examined rapidly by limited numbers of technologists. To fail to recognize a venereal disease would be as tragic now as ever before. To misdiagnose another disease as venereal in origin would be an equal calamity. The enormity of such a mistake would be self-evident in those states where premarital health certificates are mandatory. There are other equally compelling reasons why absolute laboratory proofs are needed.

In recent years it has become obvious that the emergence of numerous laboratory tests for venereal disease has created a further dilemma for the clinician. During the past decade alone more than a dozen new laboratory procedures have been introduced. The very fact that they have come along must indicate that most of them could not have been too reliable. Before the clinician has become accustomed to a new test, another appears. In some laboratories one type of test prevails. In another a second test is more popular. A third laboratory seems to express a preference for yet another procedure. Why this seeming confusion? Which test should the doctor request? What would the results signify? The following explanations may be pertinent.

Syphilis

The tests for syphilis may be classified as follows:

(a) Direct visualization of *Treponema pallidum*
(b) Identification of Treponema antibodies
(c) Tests for non-Treponemal reagins
(d) Nonspecific indicators of local disease
(e) Characteristic histopathologic lesions

There is greatest doubt over the tests for antigens and reagins, which I shall attempt to clarify. However, the significance of direct identification of *Treponema pallidum*, appreciation of the value of nonspecific indicators of local disease, or the importance of histopathologic recognition of specific lesions should not be underemphasized.

Direct identification of Treponema pallidum. The standard method is dark-field microscopy. In exudate from a syphilic chancre the organism is clearly visible under this optical system and presents as a slender, motile, rotating, rigid spirillum with close regular curves. Ulcerating lesions, whether syphilitic or nonsyphilitic, may yield other spiral organisms on dark-field microscopy. These include *Treponema microdentium, T. macrodentium, Borrelia vincentii, B. recurrentis, Spirillum minus, Treponema pertenue, Treponema herrejoni,* and *Leptospira ictero-*

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haemorrhagiae. To the novice, diagnosis may therefore present quite a problem. The expert will usually encounter little difficulty in recognizing *Treponema pallidum*. There are certain limitations to these tests, chief of which is that the *Treponema pallidum* cannot be stored long, nor can it be cultured. It must therefore be recognized at the clinic, and this implies either the availability of technical personnel or competence in dark-field microscopy on the part of the physician. Both these requirements often are not met.

Delayed dark-field examination. This can be made if it is possible to collect chancre serum in 2 mm. capillary tubes. After sealing their ends in paraffin wax these tubes can be sent to a nearby laboratory for dark-field microscopy.

India ink method. This is a simple test which often works surprisingly well. The India ink is mixed with the serum. If spirochetes are present they show up white against the black ink background. The picture is similar to that of dark-field microscopy.

Nigrosin method. *Treponema pallidum* may also be identified under oil immersion microscopy after staining with nigrosin formalin on an air-dried drop of exudate on a glass slide.

Fontana's stain. An air-dried smear may also be fixed in glacial acetic acid and formalin, steamed in a tannic acid-phenol mordant, and exposed to dilute silver nitrate and ammonia. The *Treponema pallidum* has a specific affinity for the silver which selectively precipitates on the organism, thus rendering it clearly visible on microscopy.

Fluorescent antibody methods have recently been explored as a means of identifying *T. pallidum*. These have the drawback of needing expensive fluorescence microscopic equipment generally not available at the clinic level. This principle of fluorescence is again used in the FTA-ABs test to be discussed, with the important distinction, however, that the spirochete visualized in the FTA-ABs test is artificially introduced and is not that of the patient.

Electron microscopy. This is an elegant method of demonstrating the spirochete which is seen to be a wavy organism with a distinct envelope and with short fibrils arising at irregular intervals from the body of the spirochete. This is the description for the *T. pallidum* usually responsible for venereal syphilis. Other spirochetes have other characteristics. For instance, the Reiter treponema has clusters of fibrils arising near the tips of the organism but not from the body.

Nonspecific indicators of syphilis. These clues are often underestimated. An unexplained albuminuria may furnish the lead that there is syphilitic damage of the kidneys. Lymphocytosis and particularly plasmacytosis is often associated with syphilis. Changes in the protein content of the cerebrospinal fluid furnish evidence of cerebral damage by the spirochete. This protein change is the basis for the Pandy test, which requires precipitation of the protein by either saturated phenol solution or by sulfosalicylic acid. The amount of precipitate can be mensurated against a known standard solution by means of an appropriate photoelectric colorimeter.

Serodiagnostic tests. The serologic tests for syphilis are of 2 basic categories (table 1), Treponemal antigens and tests for non-Treponemal reagins:

TABLE 1: Serodiagnostic Tests for Syphilis

A. Treponemal antigen tests
    e.g. TPI
        FTA—ABs

B. Non-Treponal reagin tests
    1. Complement-fixation
        e.g. Wassermann
            KRP

    2. Flocculation
        e.g. Kahn
            VDRL

Treponemal antibodies. These are circulating antibodies formed by the host against the *T. pallidum* itself. These antibodies are of the same type and significance as antibodies to most parasites, bacteria, fungi and viruses and may represent attempts of the host to acquire immunity to the invading parasite. These antibodies are species- and strain-specific. This is to say that for every strain of *Treponema pallidum* there is a distinctive antibody. For every other Treponema strain there is another specific antibody. To identify these antibodies there are more than a dozen methods, ranging from TPI to the FTA-ABs tests (table 1). These will be discussed below. However, in spite of the availability of these relatively specific tests there are many residual problems. Currently, for instance, there are on record 129 cultivatable strains of Treponemata. There should be as many types of antibodies. The chimpanzee of Africa, which is extensively used in syphilis research, is infected with a treponeme which is morphologically indifferentiable from *T. pallidum* of man except in terms of antibodies. This treponeme may be the same organism as that which causes yaws in man. The chimpanzee has been experimentally infected with *Treponema cuniculi*, the agent of rabbit syphilis.

Non-Treponemal reagins. These are antibodies to non-nitrogenous phospholipid host substances. They therefore differ from the specific antibodies to the treponeme just discussed. Reagins accumulate in the blood as a result of the interaction of the *Treponema pallidum* with the host tissues. Reduced to their simplest form these non-Treponemal reagins may be defined as globulin-type reactive substances produced by the host in response to the emergence of abnormal host substances at the sites of syphilitic lesions. To comprehend this concept more clearly it should be recalled that the *T. pallidum* causes extensive local and diffuse cell damage. In their crudest form these manifestations of the pathogenic, toxic, or parasitic action of the Treponema are ulcerative (chancre, gumma), inflammatory (macular, papular and mucous) and fibrogenic lesions (cardiovascular scarring, hepatocirrhosis, nephrosclerosis). These lesions are familiar to the clinician and pathologist. Their inapparent immunologic counterparts are the phospholipid substances which result from the breakdown of cells at the sites of the syphilitic lesion. Antibodies are formed by the host to these breakdown products. These antibodies are the reagins.

Flocculation tests. Flocculation tests demonstrate the presence of macromolecular 7S and 19S globulin reagin complexes characteristic of syphilis. These tests are relatively simple to perform in a standardized way and are therefore suitable for epidemiologic screening of large population groups. They are also relatively sensitive. If syphilis is present these tests are almost certain to indicate this. However, they are relatively nonspecific. If the test yields a "reactive" result this would probably signify syphilis but could also be due to the presence of a variety of nonsyphilitic diseases. This is due to the fact that these tests prove only the existence of macromolecular reagins in the blood. Similar globulin-type macromolecules are produced during the course of many nonsyphilitic diseases, thus producing biological false-positive reactions.

The available flocculation tests are enumerated in table 2. Of these tests the Kahn test is the prototype and the VDRL the currently most standardized and universally acceptable test. The Kahn test used powdered beef heart extract with added purified cholesterol as the reagent. All the succeeding tests have used various combinations of cardiolipin, lecithin and cholesterol with chemical modifications to improve their standardization, stability and sensitivity. The Kahn test has gone out of vogue because it was the least sensitive although exceedingly useful when first introduced. Of all the tests, as

TABLE 2: Flocculation Tests for Syphilis

Test	Year	Reagents—Per cent			Other
		C	L	Ch	
Kahn	1940*	?	?	0.6	Powdered beef heart
VDRL	1948	0.03	0.21	0.9	Benzoic acid; formaldehyde Na_2HPO_4; KH_2PO_4; NaCl
Hinton	1948	0.0884	0.6188	0.24	NaCl; glycerine
Kline	1949	0.2	1.8	1.0	C_2H_2OH; NaCl
Mazzini	1951	0.025	0.2	0.75–0.9	NaCl; KH_2PO_4; Na_2HPO_4; HCl; formaldehyde
RPR†	1957	0.03	0.21	0.9	Ethylene dinitrillotetra-acetic acid
USR†	1960	0.03	0.21	0.9	Phosphate; Merthiolate®; choline chloride
PCT‡	1961	0.03	0.21	0.9	Benzoic acid; formaldehyde; NaCl; Na_2HPO_4; KH_2PO_4

C = Cardiolipin
L = Lecithin
Ch = Cholesterol
VDRL = Venereal Disease Research Laboratory test.
RPR = Rapid plasma reagin.
USR = Unheated serum reagin.
PCT = Plasmacrit modification of VDRL.
* Dr. Kahn described his method first in 1925.
† Portnoy et al.
‡ Andujar and Mazurek.

TABLE 3: Dilution Sensitivity of Flocculation Tests

Dilution*	Kahn	VDRL	Kline	Mazzini	Hinton
1-1					
0.8-1.2					
0.7-1.3	R				
0.6-1.4		R	R		
0.5-1.5				R	R
0.4-1.6	—WR—				
0.3-1.7		—WR—	—WR—		
0.2-1.8				WR	
0.1-1.9					WR
0.0-2.0	N	N	N	N	N

* Reactive/nonreactive serum ratios.
R = Reactive
WR = Weakly reactive
N = Nonreactive

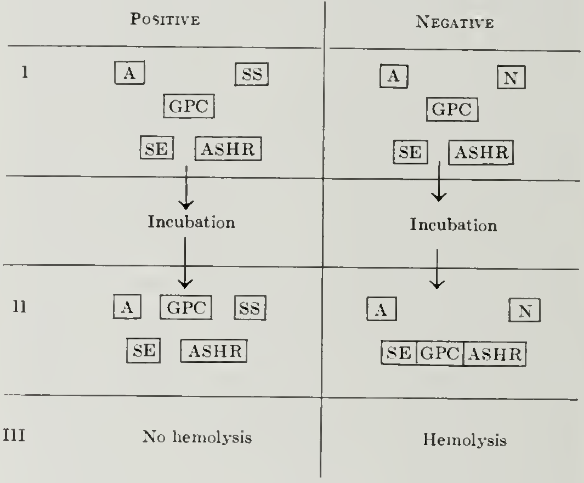
shown in table 3, the Hinton is the most sensitive. The VDRL has, however, progressively replaced all the tests, even though it is only slightly more sensitive than the Kahn test. In recent years the VDRL test has been modified to make it available for use in the branch laboratory rather than in the serologic department. USR, PCT, RPR, and CT variations are less reliable than the VDRL, but easy to apply and interpret. They include the unheated serum reagin (USR) or the rapid plasma reagin of Portnoy (RPR). The latter has been further adapted as a card test (CT) and is particularly useful in mobile screening units. The plasmacrit test (PCT) was devised by Andujar and Mazurek for office procedures as it can be applied to a drop of blood obtained from a finger for blood count and hematocrit purposes.

Complement-fixation tests. The principle of complement-fixation furnished diagnostic laboratories with the first serologic test, namely, the Wassermann reaction (1906). Wassermann used as his principal reagent source the liver of syphilitic human newborns. Although the WR held sway for about 4 decades, it has been totally modified. Nevertheless, the principle remains the same.

The reagins produced by the host in response to the release of phospholipid breakdown products in syphilitic lesions include small molecule globulin moieties in addition to the macromolecules already discussed in connection with the flocculation tests. These micromolecules, as they may be called for convenience, are not able to produce precipitin reactions and therefore do not contribute to the flocculation test. They do, however, have the capacity to bind normal complement in the presence of syphilis-specific antigen. The micromolecular reagins may therefore be identified by means of the complement-fixation tests. Although the reagin is nonspecific, the antigen can be made relatively specific, e.g., Reiter treponeme protein. A positive reaction is therefore more definitely confirmatory of syphilis than is that obtained through a flocculation test.

Currently the Kolmer complement fixation (KCF) or the Kolmer-Reiter protein (KRP) are the most popular tests. The basic principle of these tests is summarized in table 4. If syphilis is present the patient's serum will contain the specific micromolecular reagin, which will become fixed to the cardiolipin or the Reiter protein antigen through the intermediacy of the complement in guinea-pig serum. No complement will then be available to activate the hemolytic system. Hemolysis therefore does not occur. The complement-fixation test now is positive. This means that evidence of syphilis has been produced. If syphilis is not present, the antigen and patient's serum will not fix the guinea-pig complement. The latter then is left free to unite with the sheep-cell amboceptor system with resultant hemolysis of the sheep erythrocytes. Hemolysis then signifies that the complement fixation is negative. Syphilis therefore probably is not present.

TABLE 4: Complement-fixation Tests for Syphilis



A = Antigen, i.e. extract of beef heart (Kolmer) or extract of avirulent—Reiter strain *Treponema pallidum* (RPCF)
SS = Syphilitic serum with specific reagin.
GPC = Normal guinea-pig serum complement.
SE = Sheep erythrocytes suspended in saline solution.
ASHR = Antisheep hemolysin (amboceptor). Blood serum from a rabbit which had received repeated injections of sheep erythrocytes.
N = Normal blood without syphilitic reagin.

The simplicity of this schema poses the question why the Kolmer-Reiter protein complement-fixation test is not the final answer to the laboratory diagnoses of venereal syphilis. There are 2 reasons why the KRP test is not used routinely or exclusively. First, the preparation of the component reagents is an elaborate process and requires a degree of technical expertise not always available in sufficient abundance. Second, the patient's blood may contain anticomplementary substances other than the syphilitic reagin so that an abnormal result may be achieved. Finally, in about 20 per cent of cases micromolecular reagins are not yet present in sufficient concentration to yield a positive complement-fixation reaction. The introduction of the treponeme-derived Reiter protein antigen has reduced the margin of error, but even this Reiter protein is only generically and not species specific, whereas the syphilitic reagin is species- and strain-specific. The need for additional confirmation tests therefore persists.

Treponemal tests. The evolution of these tests has been summarized in table 5. The very fact that there are so many tests betrays the existence of fallacies. Yet these tests should come closest to precise diagnosis since they depend on laboratory identification of species- and strain-specific host antigens to substances in the capsule of the treponeme. The latter are lipopolysaccharide complexes in the envelope of the body of the spirochete but may exclude antigenic complexes residing in the filaments attached to the body of the treponeme. The strain or type characterization of treponemes may be linked to these fibrils. This explains why non-venereal treponemes, such as the Reiter treponeme, may serve as useful diagnostic tools for demonstrating the existence of venereal syphilis.

TABLE 5: Treponemal Antigen Tests for Syphilis

I. Antigen of wholebody virulent *T. pallidum* (Nichol's strain)	
A. Viable spirochetes	
(i) TPI (1949)	*Treponema pallidum* immobilization
(ii) TPMB (1956)	*Treponema pallidum* methylene blue
B. Nonviable spirochetes	
(i) TPA (1953)	*Treponema pallidum* agglutination
(ii) TPIA (1953)	Treponema immune adherence
(iii) WTPCF (1956)	Wholebody *T. pallidum* complement-fixation
(iv) FTA (1958)	Fluorescent Treponemal antibody
(v) FTA 200 (1960)	Ditto at 1/200 dilution using fluorescein isothiocyanate
(vi) FTA—ABS (1965)	Fluorescent Treponemal antibody absorption
II. Antigen of chemical fractions of wholebody virulent *T. pallidum* (Nichol's strain)	
A. TPCF (1955)	*Treponema pallidum* complement fixation
B. TWR (1957)	Treponemal Wassermann reaction
C. TPCP (1958)	*T. pallidum* cryolysis protein
III. Antigen of chemical fractions of wholebody *Reiter Treponeme*	
A. RPCF (1957)	Reiter protein complement-fixation
B. KRP (1958)	Kolmer complement-fixation test with Reiter protein antigen

Of the number of treponemal antigen tests defined in table 5 the TPI has long stood up as the most specific for venereal syphilis. This test (and also the TPMB) uses as the antigen whole-body Nichol's strain *Treponema pallidum* under appropriate conditions. These treponemes are rapidly immobilized by the treponemal specific gamma globulin of syphilitic serum. A reactive result therefore indicates that the patient probably has syphilis, and a non-reactive result signifies that he probably does not have syphilis, but we cannot be absolutely sure since there are possibilities of error. The TPI has the further disadvantage of being difficult to perform with absolute perfection. An adequate rabbit colony must be maintained to provide a source of viable treponemes; the technology must be very precise and the thioglycolate must be perfectly standardized, etc. There are many points at which minor variations from standards would lead to false results.

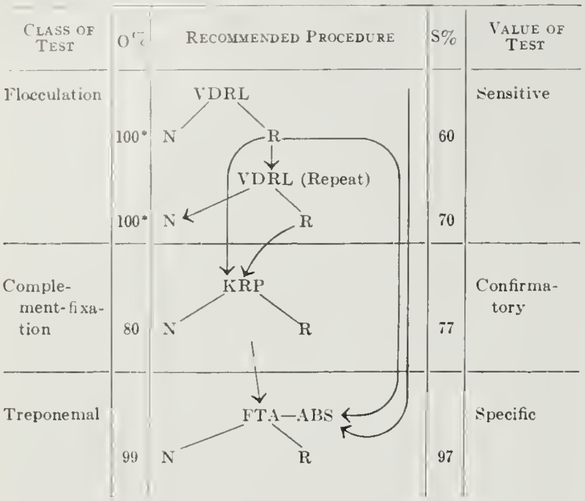
To overcome the difficulties produced by the need for viable virulent *T. pallidum*, the *Treponema pallidum* agglutination (TPA), the *T. pallidum* immune adherence (TPIA), and the whole body *T. pallidum* complement-fixation (WTPCF) tests were introduced. These tests can be conducted with nonviable spirochetes. With the introduction of the concept of fluorescence microscopy, the FTA (fluorescence treponemal antibody), FTA 200 (fluorescence treponemal antibody performed at a 1/200 dilution because of the introduction of fluorescein isothiocyanate), and finally the FTA-ABs (fluorescent treponemal antibody absorption test) were made possible. The last appears likely to prove the most reliable specific test.

In the meanwhile other treponemal tests have been tried. Antigens derived from biochemical fractions of the Nichol's *T. pallidum* formed the basis for the TPCF (*T. pallidum* complement-fixation), TWR (treponemal Wassermann reaction), and the TPCF (*T. pallidum* cryolysis protein) tests. As is evident, these tests are complement-fixation tests exploiting extraneous treponemal antigens as reagents. Similar tests also were devised by means of biochemical fractions of the Reiter protein avirulent treponeme (RPCF) and KRP. These have already been discussed under the heading of Complement-Fixation Tests. It should be stressed once more that the treponemal components used in these tests are artificially added to the reaction and do not represent the infecting spirochetes which are the cause of syphilis in the case under investigation.

Serodiagnostic tests of election. Which of the score of tests should we use today? In table 6 a schema has been prepared to show how a difficult case may be diagnosed by using a small selection only of these serodiagnostic tests.

Of the flocculation tests the VDRL certainly is the easiest to perform. The PCT, USR, and RPR variations are practical clinical laboratory procedures. The VDRL is highly sensitive, i.e., highly likely to react in the presence of syphilis. A nonreactive finding almost certainly refutes the possibility of syphilis. However, a reactive finding may be indicative of syphilis only in

TABLE 6: Serodiagnosis of Syphilis



N = Nonreactive.
R = Reactive.
O% = Probability of absence of syphilis.
S% = Probability of presence of syphilis.
* Except in greatly delayed stages of syphilis when reagins may have vanished.

about 60 per cent of cases. This margin of error can be reduced by about 10 per cent if the VDRL is repeated.

Slightly better confirmation of syphilis may be obtained by the use of the KRP (Kolmer-Reiter protein) test for which the probability that a reactive result indicates syphilis is about 77 per cent. This test is difficult to perform and a repeated VDRL may be advantageous. False results may also be due to anticomplementary substances.

The next step is the exploration of the FTA-ABs treponemal antigen principle. This test is highly specific for syphilis. Nonreaction means the probable absence of syphilis and a positive reaction signifies the probability of syphilis in about 97 per cent of cases. Once the technique of fluorescence microscopy has been mastered, the FTA-ABs test is not difficult to execute. It probably will replace the KRP and may even be useful as a primary screening device since 1 technician can perform about 50 tests per day.

The ability of these tests to identify syphilis at its various stages varies appreciably, as shown in table 7. As is evident, the VDRL is reasonably accurate for secondary syphilis but may be significantly inadequate at the primary and tertiary stages. The KRP is slightly better for all categories, while the FTA-ABs is near perfect for the secondary and tertiary stages. In this respect the FTA-ABs is a significant improvement over the TPI, which was long held to be the most specific test for syphilis. Undoubtedly new tests will be evolved to cover all contingencies. One of these now in the experimental stage is the complement-deviation test (CDT), which is said to be more specific though less sensitive than the VDRL.

Errors. As in all technologic procedures false results may arise. These may be due to a variety of causes, either man-made or biological.

The most important source of false results is deviation from standard procedures. All the serodiagnostic tests are precisely designed. Every step has narrow tolerance limits. It takes a great deal of supervisory discipline and technician loyalty to ensure that each test is performed correctly every time. This presumes the existence of human attributes which cannot be universally or perpetually guaranteed.

TABLE 7: Sensitivity and Specificity of Serodiagnostic Tests for Syphilis

Test	Stage of Syphilis		
	1	2	3
	Per cent		
VDRL	50	80	50
KRP	60	90	65
FTA—ABs	80	100	99
TPI	30	67	99

Even when the laboratory technician is "perfect" the test can still go wrong. For instance, the reagents may have stood on the shelf too long and thus begun to decay. This may happen in the laboratory or may be the fault of the manufacturer. The latter may even furnish inadequately standardized reagents, or even worse, contaminated materials. The glassware also should not be overlooked. It may be chemically contaminated on delivery or may not have been adequately washed before re-use. To wash glassware clean requires not only a good washing machine but also clean water. All too frequently the distilled water for the final rinse is ion-contaminated, especially if the water has stood long in glass or metal containers. Finally, mention should be made of the frequency with which the blood specimen is defective. The syringe may be contaminated with alcohol or detergents; the specimen may have been delayed in transit; bacterial decomposition may have commenced, etc. The possibility of a technical error therefore always exists, and this should cause caution in accepting the laboratory diagnosis.

Biological false-positive reaction (BFP). This has for long been a major cause of concern about the validity of laboratory findings.

About 1/4,000 "normal" individuals will give a "reactive" result with the VDRL test. Even in infants the incidence of BFP reactions may be quite high because there may be passive transfer of macromolecular lipoprotein substances from the mother. Usually BFP reagins appear only after about the fifth month of infancy when intercurrent infections commence to be more frequent. The list of disease states capable of causing BFP reactions grows each year. Table 8 furnishes a representative list. All of these conditions are characterized by the existence of circulating lipoproteinaceous substances, which may act similarly to syphilitic reagins in the flocculation tests.

TABLE 8: Biological False-Positive Serodiagnostic Reactions

Condition	Frequency (Per cent)
Malaria	95
Leprosy	62
Infectious mononucleosis	29
Postdiphtheritic immunization	21
Vaccinia	20
Lymphogranuloma venereum	19
Disseminated lupus erythematosis	17
Thyroiditis	16
Infectious hepatitis	11
Periarteritis nodosa	10
Extensive carcinomatosis	9
Rheumatoid arthritis	8
Rheumatic fever	7
Pneumococcal infections	5
Common cold, pregnancy	3
Recent blood loss	2
Collagen disorders	1
Tuberculosis (some forms)	1
Narcotic addiction	1

The fluorescent antibody tests produce virtually no biologically false-positive results. This is because they do not depend on the existence of circulating macromolecular reagins. The test cannot therefore be confused with the nonsyphilitic diseases listed in table 8. The complement-fixation tests can produce false results due to the existence of anticomplementary substances. This is the chief limitation of these tests. When there is doubt, however, the deficiency can be remedied by applying an FTA-ABs test.

The FTA-ABs itself can rarely produce errors involving strain differences in treponemata. As has been mentioned, there are on record 129 strains of *T. pallidum*. The FTA-ABs is *T. pallidum* species-specific, but it cannot discriminate between those other strains which cross-react with the Nichol's strain. Some of these strains are avirulent treponemes so that it is possible occasionally to conclude from a positive FTA-ABs test that venereal syphilis is present whereas the spirochetal disease may be nonvenereal.

Because of these persistent problems the emergence of new tests should be anticipated with an attitude of acceptance rather than skepticism.

The Kolmer-Reiter protein complement-fixation test has recently been modified as a complement-deviation test (CDT) in which a lipoprotein is used as the antigen. This may help to eliminate some of the false-negative results. The test is still under investigation but has already proven more specific though less sensitive than the VDRL. Improvements of the fluorescent antibody absorption tests are in the experimental stage.

Quantitative serologic diagnosis. Nothing has been said thus far about weak-reactive readings and serologic titers.

If the laboratory report is weak-reactive, this may signify the absence of antibodies or reagins in sufficient quantity to produce an adequate reaction, or it may signify the presence of a nonsyphilitic disease, the fact of premature or prior antibiotic therapy or an error of technique. The clinician should respond to a report of "weak reaction" by submitting a new blood specimen and requesting a confirmatory alternative test or a titration report. Usually the KRP or the FTA-ABs will resolve the issue.

Titrations are tedious but easily comprehended. They constitute quantitative serology. Either the VDRL or the KRP is used for quantitation. The serologist makes dilutions of the serum and antigen in arithmetical ratios from a 1:1 to a 1:256 dilution. The level of dilution to which a flocculation or complement-fixation reaction can be attained provides evidence of the amount of reagin present, and thus the severity and the stage of the disease. The serum will contain the highest proportion of reagins at the height of the secondary stage of syphilis. After syphilis has been present many years there may be insufficient circulating reagin to produce a reactive result.

Titre data are not needed for diagnosis except when there is much doubt. A rising titre will be indicative of syphilis when the original result was in doubt. Titre data are of more value in gauging the effect of therapy and should perhaps be limited to this use.

Histopathologic diagnosis of syphilis. Before leaving the subject of the laboratory diagnosis of syphilis it would be pertinent to refer briefly to the role of histopathology. This is, of course, par excellence, a laboratory method of diagnosis.

The histologic characteristics of syphilitic lesions of various organs of the body are too well documented in textbooks of pathology to be recapitulated here. Suffice it to say that the syphilitic lesion, though capable of mimicking many other lesions, often presents quite distinctive morphologic features (table 9). The expert pathologist can frequently say with considerable assurance that a particular lesion is probably syphilitic in origin, despite the protean character of many variants of the syphilitic process.

TABLE 9: Differential Diagnosis of Syphilis

DISEASE	CAUSATIVE ORGANISM
Venereal syphilis	*Treponema pallidum*
Endemic syphilis	*Treponema pallidum*
Bejel	
Dichuchwa	
Njovera	
Yaws	*Treponema pertenue*
Pinta	*Treponema carateum*
Chancroid	*Haemophilus ducreyi*
Lymphogranuloma venereum	Lymphogranuloma venereum virus
Granuloma inguinale	*Calymmatobacterium granulomatis*

It should also be pointed out, and this is not as well documented in the average textbook accessible to clinicians, that it is quite often possible to demonstrate the treponemal organisms within specific lesions. The Levaditi stain was the first to acquire popularity. There have been many variations of this silver impregnation stain, the most successful probably that of Warthin.

Many syphilitic lesions are quite accessible for biopsy examinations. Reference is made here to not only the chancre, which is a cutaneous ulcerative granuloma, but also to the mucocutaneous secondary syphilitic lesions. There also are the regional lymph nodes. Any of these lesions could be sampled for histologic examination without any danger of aggravating the local syphilitic disease. The appearance is usually quite characteristic, and spirochetes will often be demonstrable in abundance in the lesions. In recent years attempts have even been made to identify some of these spirochetes as *Treponema pallidum* through fluorescence microscopy.

By these accessory aids a diagnosis which remains in doubt after completion of representative serologic tests may be established. It should also be recalled that syphilis may coexist with other diseases, e.g., pyogenic infection, tuberculosis, leprosy, lupus erythematosis, sarcoidosis, many skin diseases, and cancer.

Gonorrhea

The laboratory tests for gonorrhea present many problems but are less difficult and less confusing than are the procedures required for the recognition of syphilis.

For the present our diagnostic armamentarium is limited to bacteriologic identification of the *Neisseria gonorrhoeae*. There have been many abortive attempts to elaborate serodiagnostic tests for gonorrhea. Some microprecipitin tests have actually been made to work. However, these have proven to be relatively nonspecific and have shown poor correlation with severity or progression of the clinical symptoms.

Interpretation of the bacteriologic flora of the urogenital tract is more important for the diagnosis of gonorrhea than for syphilis. Table 10 presents a list of some of the organisms which can be present. About half of these are normal inhabitants of this body region. Those which are

TABLE 10: Flora of the External Urogenital System

NORMAL	ABNORMAL
Male:	*Neisseria gonorrhoeae*
Escherichia coli	*Neisseria meningitidis*
Staphylococcus epidermidis	*Haemophilus ducreyi* *Haemophilus vaginalis*
Diphtheroids *Mycobacterium smegmatis*	*Calymmatobacterium granulomatis*
	Streptococcus pyogenes
Female:	*Staphylococcus aureus*
Döderlein's lactobacillus	Anaerobic streptococci
E. coli	Mycoplasma (PPLO)
Aerobacter aerogenes	*Candida albicans*
Staphylococci	*Trichomonas vaginalis*
Streptococci Yeasts	Virus of lymphogranuloma venereum
Veillonella	Virus of herpes simplex
Mycobacterium smegmatis *Mima polymorpha oxidans*	*Corynebacterium diphtheriae*
Neisseria catarrhalis	*Treponema pallidum*
Neisseria sicca	*Mycobacterium tuberculosis*
	Vincent's fusospirillum, etc.

classified as abnormal flora are seldom found in relation to the urogenital system unless they are associated with local lesions.

Microscopy. The gonococcus is of course distinguishable by virtue of the fact that it is a gram-negative diplococcus, usually demonstrable best within leukocytes. However, this is not the only organism of comparable morphology which may be found in discharges suspected to be of gonorrheal origin. Table 11 furnishes a tabulation of the principal gram-negative cocci. The diagnostic problem is to distinguish between these. Except for *Veillonella,* which is a minute organism, all these bacteria are about the same size. *N. gonorrhoeae* is a bean-shaped diplococcus with concave adjacent sides. *N. meningitidis* is also a bean-shaped diplococcus, but the adjacent sides are flat. It takes really high-grade microscopy to tell these apart. Usually this cannot be done in the average laboratory. However, it should be reasonably possible to distinguish *N. catarrhalis* and *N. sicca,* since these are spherical diplococci with flat adjacent sides.

TABLE 11: Gram-negative Cocci

Genus	Species
Neisseria	*gonorrhoeae* *meningitidis* *catarrhalis* *sicca*
Veillonella	* *parvula* *alkalescens* *discoides*
	† *reniformis* *orbiculus* *vulvovaginitidis*

* Gas-forming.
† Nongas-forming.

Culture characteristics. The propensities of these organisms to grow on various media are summarized in table 12. *N. gonorrhoeae* and *N. meningitidis* prove to be quite fastidious. They do not grow readily on any but enriched media such as chocolate agar, and they require carbon dioxide and oxygen. Both need to be incubated before growth will occur, whereas *N. catarrhalis* will grow at room temperature. *Veillonella* will not grow in the presence of oxygen. *N. gonococcus* cannot be cultured in the absence of 10 per cent CO_2. All except *Veillonella* are oxydase-positive (1 per cent para-aminodimethylaniline monohydrochloride).

Fermentation. The organisms can be further identified by sugar fermentation procedures. Table 13 shows that *N. gonorrhoeae* and *N. meningitidis* both ferment dextrose but not glucose or sucrose. *N. gonorrhoeae* does not ferment maltose, whereas *N. meningitidis* does. *Veillonella* ferments only glucose and may cause the evolution of gas and acid. *N. catarrhalis* is nonfermentative. *N. sicca* ferments all sugars. In practice these fermentation procedures can only be applied in rare instances. The majority of state laboratories receive too many suspected gonorrhea specimens daily to be able to offer this refinement as a diagnostic aid. Further special or confirmatory data can be furnished in isolated cases by the use of Thompson's test (rapid solubility of *N. gonorrhoeae* in N/10 sodium hydroxide solution). The *N. gonorrhoeae* can also be specifically identified by an agglutination test with the use of serum from chickens hyperimmunized by virulent *N. gonorrhoeae.*

TABLE 13: Gram-negative Diplococci
Sugar Fermentation

Organism	Dextrose	Glucose	Maltose	Sucrose
N. gonorrhoeae	+	−	−	−
N. meningitidis	+	−	+	−
N. catarrhalis	−	−	−	−
N. sicca	+	+	+	+
Veillonella	−	+	−	−

TABLE 12: Cultural Characteristics of Gram-negative Diplococci

Organism	Growth Potential					Colony (mm.)	Oxidase-positive	Hemolytic
	Ordinary Media	Chocolate Agar	Room Temperature	Requirement CO_2	Anaerobic			
N. gonorrhea		+		+		1–4	+	
N. meningitidis		+		+		1–4	+	
N. catarrhalis	+	+	+			2–5	+	
N. sicca	+	+	+			Dry crumbling	+	(+)
Veillonella	+	+			Obligate		−	+

Gonophage identification of *N. gonorrhoeae* also is possible. The gonococcus will undergo lysis on incubation in the presence of this gonophage. All these tests, however, are elaborate to conduct and quite unsuitable for screening large population groups.

Virulence characterization. In addition to these identifications some form of virulence test and a drug sensitivity test would be needed for a complete diagnosis in a case of suspected gonorrhea.

There is increasing evidence that virulent gonococci may be transformed into organisms of low or negligible virulence as a result of their exposure to the DNA (desoxyribonucleic acid) of the host. The reverse may also be possible.

Drug sensitivity. Penicillin remains the drug of choice for the therapy of gonorrhea. Drug resistance has, however, been noted, and in some regions this has attained to as high as 54 per cent of cases. Whether this is true penicillin resistance or evidence of premature or self-treatment with penicillin before a laboratory diagnosis is sought remains to be determined.

Thayer-Martin technique. The main laboratory problem thus far has been the need for processing large numbers of specimens through laboratories which are all too often understaffed. This problem has been largely reduced by the recent modifications of the enriched media introduced by Drs. Thayer and Martin of the Communicable Disease Center. The principle exploited involves the incorporation of chemicals in the medium which will suppress the growth of saprophytic Neisseria and of other organisms. Originally ristocetin and polymyxin B were used, but ristocetin was later withdrawn from the commercial market, so that the new formulation (VCN) comprises vancomycin, Colistimethate® and nystatin. These chemicals suppress the growth of all of the saprophytic Neisseriae, Veillonella, Mima, yeasts and staphylococci. *Bacillus proteus* will still grow on this VCN medium, but since it reacts negatively to the oxidase reagent the gonococcal colonies are readily differentiated, since they are the only colonies which will turn black after the oxidase reagent has been added. These cultures still require 24 to 48 hours of incubation in a 10 per cent CO_2 environment at 35–36°C. Apart from this inconvenience the use of the VCN medium has eliminated 2 major steps in the laboratory diagnosis of gonorrhea. It is no longer imperative to scan cultures for the presence of gram-negative diplococci. Nor is it necessary to conduct a fermentation test. This has greatly simplified the laboratory task.

At the clinic or in the physician's consulting room the substitution of VCN culture methodology for the slide method may cause a little extra work, since streaking and shipping of culture plates may be a little more laborious than the preparation of smears on glass slides. For the time being smears will therefore continue to come to the Health Department laboratory by the thousands. The shipping problem is being worked out presently. Once an incubator container which will not only keep the streaked VCN culture warm and moist but under 10 per cent CO_2 coverage has been refined every clinician should be able to mail in cultures instead of slides for identification. Theoretically it should even be possible to devise small field incubator kits and built-in oxidase mechanisms so that the clinician would be able to read his culture plates directly. This will finally solve the problem of the laboratory diagnosis of gonorrhea by converting it into a "quicky" office procedure.

TABLE 14: Diagnostic Laboratory Criteria

Neisseria gonorrhoeae

A. Slide preparation
    (a) Gram-negative, bean-shaped diplococci with concave inner surfaces, within polymorphonuclear leukocytes.
    (b) Positive green fluorescence on an orange background with the FITC procedure.
B. Chocolate agar culture
    (a) Shiny, discrete, moist colonies, 1–4 mm. in diameter, containing gram-negative diplococci.
    (b) Oxidase positive*.
    (c) Growth does not initiate at 22°–26°C.
    (d) Carbon dioxide and oxygen needed for primary isolation.
    (e) Ferments dextrose but not maltose or sucrose.
C. Thayer-Martin VCN culture†
    (a) Oxidase-positive* colonies

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* 1 per cent Di- or tetramethylparaphenylene diamine hydrochloride.

† *N. meningitidis* may grow on this medium but can be excluded by agglutination and fluorescent antibody methods.

Fluorescence microscopy. Reference should finally be made to the fluorescent antibody method of identifying the gonococcus. By counterstaining the prepared smear with Evans blue the background fluorescence is quenched so that the fluorescing antibodies attached to the gonococcus clearly reveal these organisms. The FITC

(*Continued on page 404*)

The Diagnosis of Early Syphilis*

SIDNEY OLANSKY, M.D., F.A.C.P.†

EARLY SYPHILIS includes primary syphilis, secondary syphilis, and latent syphilis up to 2 years. These are the infectious stages of the disease and are most important to recognize because treatment in these stages will prevent spread of the disease and offer the best prognosis to the infected individual.

Primary Syphilis

Infection occurs immediately on contact with an infected individual, but the first clinical manifestations do not appear for about 3 weeks. The primary lesion (chancre) usually appears in the anogenital area, but it may appear on the finger, lip, toe, breast, etc., depending on how the disease was acquired. The chancre is usually a single, eroded, indurated papule which is painless and is usually associated with a discrete rubbery painless lymph node (satellite bubo) in the drainage area of the lesion. Although most chancres are as described, they may be soft or ulcerated or multiple. Any lesion in the anogenital area is suspect.

If the site of the chancre is such that the lymph nodes are not palpable, i.e., chancre of the anus, the satellite bubo may not be detected.

Dark-field examination permits an exact diagnosis of syphilis since the causative organism can be demonstrated directly by this means. Unfortunately, spirochetes on the surface may readily disappear on the application of antiseptics or small doses of penicillin, and these may render the examination negative. A positive dark-field examination is diagnostic, a negative one may not rule out syphilis.

The chancre will heal spontaneously in 2 to 3 weeks without therapy. This may lead some patients to think that they are cured, which is unfortunately not true.

Primary syphilis may be associated with a nonreactive serologic test for syphilis (STS) or a reactive one. The former is called seronegative primary syphilis, the latter seroreactive primary syphilis.

Differential diagnosis. Many penile lesions are not syphilis, and the following are some conditions which must be differentiated:

Chancroid. These are usually multiple painful ulcers. *B. ducreyi* can be demonstrated by spread or culture. Dark-field examinations and STS are negative. A patient with chancroid may also have syphilis, and it is possible for an individual exposed and infected with chancroid and syphilis at the same time to be diagnosed and treated and cured of his chancroid before the incubation period of the chancre has elapsed. It is desirable to follow these patients clinically and serologically for several months.

Granuloma inguinale. A single early lesion may resemble chancre, but careful observation will reveal that the lesion has been there for weeks or months, has granulations on it, and does not tend to heal. Tests for syphilis are negative. A positive diagnosis may be made by demonstrating Donovan bodies from the lesions.

Lymphogranuloma venereum. In this disease the primary lesion is vesicular and evanescent. Tests for the other venereal diseases are negative, and subsequently the appearance of inguinal nodes will make the diagnosis recognizable.

Trauma. All tests for venereal disease are negative.

Herpes progenitalis. There is usually a history of recurrent vesicles. All tests for syphilis are negative. If these patients are sexually active, they may ultimately acquire syphilis. We must, therefore, not assume that the diagnosis is always herpes, and appropriate tests for syphilis must be done repeatedly.

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Carcinoma. Early carcinoma may resemble a chancre, but biopsy will resolve the dilemma.

Other penile lesions such as fixed drug eruptions, psoriasis or lichen planus may be confusing, but the appropriate tests applied will usually clarify them.

Secondary Syphilis

Clinical manifestations of secondary syphilis are varied and diverse. There may be constitutional symptoms such as fever, malaise, sore throat, etc., but the diagnosis is usually made on the basis of lesions of the skin and mucous membranes. Cutaneous lesions may be large or small, few or many, macular, papular, papulosquamous, and occasionally pustular. They are never vesicular or bullous except in early congenital syphilis. The lesions are generally bilateral and symmetrical and not pruritic. Moist papules (condylomata lata) frequently occur in the anogenital region, the mouth, or other intertriginous areas such as the axilla, toe webs, etc. These lesions have spirochetes teeming in them, whereas the generalized lesions are dry, and demonstration of treponemes from them is difficult or impossible.

The STS are always reactive in secondary syphilis.

Special lesions seen in secondary syphilis are mucous patches in the mouth and throat, a peculiar alopecia ("moth-eaten"), and iritis. When these occur, in most instances other diagnostic lesions of secondary syphilis will also be present. Secondary syphilis is more highly contagious than primary syphilis, because there are more lesions from which spirochetes may be transmitted. Secondary syphilis will also heal spontaneously.

Differential diagnosis. Pityriasis rosea. This disease may be confused with secondary syphilis. It is usually seasonal, may be pruritic, condylomata lata do not occur, and the STS is negative.

Drug eruptions. There is usually a history of drug ingestion. The lesions are explosive and usually pruritic. A patient with early syphilis, undiagnosed, may be given penicillin for a sore throat which may be followed in 4 to 6 hours by a fever and an eruption. This is a Herxheimer reaction due to destruction of spirochetes and not an allergic drug reaction. An STS in these patients will usually show a reactive STS in a reasonably high titer.

Psoriasis. The lesions may look like those of syphilis and vice versa. In psoriasis there is usually a history of chronicity, and the STS are negative.

Lichen planus. When lichen planus is generalized the lesions are violaceous, pruritic, and characteristic; when confined to the mouth and genitalia they may cause confusion. The STS and dark-field examination are negative.

Many other eruptions may have to be considered in differentiating secondary syphilis, but the STS and the darkfield examination will usually establish the correct diagnosis.

Latent Syphilis

In this stage there are no clinical signs of syphilis, merely a reactive STS. A careful history may be helpful but is difficult to obtain. This stage must be differentiated from the so-called biologic false-positive reaction. Serodiagnosis will be discussed in another paper, and I shall not go into detail on this, but this is the area in which treponemal tests can help. The TPI test (*Treponema pallidum* immobilization) or the FTA test (fluorescent treponemal antibody) are reasonably specific.

If a biologic false-positive reaction is suspected, a reactive TPI or FTA test will rule in syphilis and a negative will make a biologic false-positive reaction likely.

Early latent syphilis is potentially infectious in that infectious relapse is possible in this stage.

Summary

Early syphilis, i.e., primary, secondary or early latent, is infectious or potentially so. The dark-field examination is the most diagnostic test in syphilis, and it can be used in primary and secondary syphilis.

The standard tests are very adequate in primary and secondary syphilis, especially if used along with the dark-field examination.

Latent syphilis may require a treponemal test to rule out biologic false-positive reactions.

It is most important to diagnose and treat syphilis when it is early, because treatment at that stage protects both the individual and the public best and is our best hope of eradicating the disease.

The Diagnosis and Management of Gonorrhea*

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THE PROBLEM OF GONORRHEA is an ancient one and reflects man's continuing struggle against disease and himself. The gonococcus has the advantage of time (a short incubation period of 3 to 5 days or less), a fertile habitat which has not been equaled by any culture medium (the male urethra or female genital organs). It possesses unlimited resources in manpower (men, women, and children with almost no age limit) and the terrifying potential of being able to enlist the same victims repeatedly. It employs the element of stealth and is given comfort by complacency, ignorance, and the frailties of man. In addition, the gonococcus has developed more resistant strains capable of challenging our most effective drugs.

The diagnosis of gonorrhea poses no involved problem in the male patient with a frank purulent urethral discharge and history of recent sexual exposure. Spreads or smear from the exudate will readily reveal gram-negative intracellular or extracellular diplococci. If antibiotics have been taken several hours prior to the examination the gonococci will appear swollen, have lost their morphologic and tinctorial characteristics, or have even disappeared.[1] One must be aware that organisms of the species, *Tribe mimeae*, while occurring normally as short, gram-negative, encapsulated, pleomorphic rods, may assume the form of diplococci identical to the gonococcus in size and appearance.[2] Some species may even mimic the gonococcus further in cultural characteristic in that they may ferment glucose alone.[2] These organisms have been isolated from patients with a variety of diseases including vaginitis, septicemia, endocarditis, meningitis, conjunctivitis, synovitis, and from the spinal fluid.[3] The normal skin serves as a reservoir for *Tribe mimeae* where they may persist in such sites as the axillae and toe web.[4] Other nonspecific organisms, Trichomonas and the virus of lymphogranuloma venereum, may also induce urethral and cervical discharge. An erroneous diagnosis of gonorrhea may not be revealed until repeated injections of penicillin provide no relief of symptoms and force a reappraisal of the diagnosis or lead to another misconception that we are dealing with penicillin-resistant gonorrhea.[5]

Spreads for the gonococcus may be used to advantage in the diagnosis of vulvovaginitis in children and acute gonorrhea, particularly urethritis in the female. As the infection becomes subacute or chronic, cultural methods must be relied upon.

The diagnosis of gonorrhea in the male homosexual is quite frustrating. On rare occasions the resulting rectal discharge may be collected from the perianal area. In most instances the patient complains of anal burning and discharge but exhibits no objective symptom. It is then necessary to resort to proctoscopy which reveals an edematous and acutely inflamed anal skin and rectal mucosa covered with thick purulent exudate.[6] Spreads secured from this purulent discharge will reveal gonococci. In subacute cases it may be necessary to dislodge the organisms from the anal crypts.

Complications such as arthritis, meningitis, and endocarditis are much more difficult to diagnose and require special techniques such as joint aspiration, spinal puncture, culture of joint and spinal fluids, and blood, etc. While these complications are rare they probably occur more frequently than suspected. A report of gonococcal arthritis with pericarditis was recently published.[7]

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Cultural techniques are used to best advantage in the diagnosis of gonorrhea in the female although culture failure rates may range from 25 to 50 per cent.[8] A new culture medium recently developed by Thayer and Martin has selective properties for the growth of the gonococcus while inhibiting the bacterial flora found in the vaginal and rectal tracts.[9] This medium containing ristocetin and polymyxin B inhibits the growth of nonpathogenic Neisseria and *Mima polymorpha varidans.*

It is well to remember that, in taking cultures from the female, specimens should be obtained from the urethra, cervix, Bartholin's and Skene's glands. The labia should be spread apart with the fingers and the vestibule wiped clean with dry sterile cotton. The urethra is then stripped toward the meatus with a finger of the other hand in the vagina and the secretion obtained cultured. The cervical plug should be removed, compression applied to the cervix with the blades of the speculum moistened with a little water and no lubricant, and a specimen taken from the endocervix. The orifices of Bartholin's glands should be cleaned and each gland compressed between the index finger within the vagina and the thumb and any secretion cultured. Positive cultures are best obtained in the female during the menstrual period. Examination of the female for gonorrhea should be encouraged at this time rather than postponed.

Deacon et al[10] were able to develop a fluorescent antibody test for the detection of the gonococcus in 1959. The fluorescent antibody test comprises a direct and an indirect test. In the former the smear is examined directly, while in the latter the gonococci are cultured and spreads taken from this culture. The principle of the FA test is an antigen-antibody response, the presence of which is detected by the addition of a conjugated fluorescein dye to globulin fractions of gonococcal K-antigen immune serum. Under ultraviolet microscopy the gonococci will fluoresce. Fluorescent antibody cultures differentiate the gonococcus from *Tribe mimeae.*

An attempt is being made to facilitate the diagnosis of gonorrhea by a complement-fixation test, but standardization of the antigen has proved difficult. A negative result does not preclude the absence of gonorrhea, while a positive result may be obtained 4 to 6 weeks following the infection.[11] This test would be of inestimable value in the diagnosis of the asymptomatic female and in male homosexuals.

It has been confirmed that the asymptomatic female patient is capable of producing gonococcal urethritis in males under experimental conditions. Brown et al[12] were able to transmit gonorrhea to volunteer male prisoners by inoculating them intra-urethrally with cervical swabs or cultures taken from asymptomatic female patients. It has also been established that gonococci may be harbored by male patients with inapparent or subclinical infections who are contacts to symptomatic females.[13]

Penicillin remains the drug of choice in the treatment of gonorrhea. However, the problem relates to dosage and the type of penicillin to be administered. It was reported in 1955 that the penicillin sensitivity of gonococcal strains ranged from 0.005 to 0.2 units of penicillin G per mm. with 20 per cent of the strains requiring 0.1 to 0.2 units per mm. to inhibit growth in vitro. In 1961 the upper limit had reached 0.7 units of penicillin per mm., and 32 per cent required 0.3 to 0.4 units per mm.[14] Penicillin should be administered in sufficient dosage to insure serum levels in excess of the minimal inhibitory concentration for any strain of the gonococcus which may be encountered. Penicillin preparations which effect a high initial concentration and sustain adequate serum levels for 48 hours are preferred.[15] Levels longer than 48 hours may even be important to assure adequate exposure of the gonococcus to the antibiotic in the female.[16] The dosage suggested by the USPHS ranges from 2.4 to 4.8 million units of procaine penicillin in aqueous suspension given at one time. When such complications as arthritis or endocarditis are present, large doses of 2.4 to 20 million units of aqueous penicillin daily are recommended until symptoms have subsided for 24 hours.[8] All sexual contacts including homosexuals should be treated prophylactically within 24 hours if possible to avoid reinfection or ping-pong gonorrhea. Recheck cultures should be taken weekly for 3 weeks in the male and monthly during the menses in the female for 3 months whenever practicable. Serologic test for syphilis should be performed on the initial visit and at the end of 3 months. It should be remembered that antibiotics may prolong the incubation period of a concomitant syphilitic infection.

Alternate antibiotics in the treatment of gonorrhea include streptomycin, 1–2 Gm. intramuscularly, and chloramphenicol, 1 Gm. intramuscularly.[8, 17] Both drugs should be administered with caution because of their toxicity and the possible development of resistant strains of organisms. Among the oral antibiotics recommended are the tetracycline compounds, erythromycin, and triacetyloleandomycin given in doses of 500 mg. 4 times a day for a total of 3 Gm.[8, 17, 18] It may be advisable to continue this treatment for at least 4 days in the female to prevent the development of resistant strains and sensitization to the antibiotic. Spectinomycin Sulfate® in dosage of 2 Gm. intramuscularly may be of value.[19]

Some of the reasons listed for the failure of penicillin to cure gonorrhea are incorrect diagnosis, reinfection, increased resistance of the particular strain of gonococcus to penicillin, inadequate serum or tissue levels due to absorption and excretion, and inadequate natural defensive mechanism of the body.[8]

With a progressive increase in resistance to penicillin by gonococcal strains and concomitant escalation of the dosage of penicillin to be administered the time may come when it may be impractical to prescribe such large doses of penicillin in the treatment of gonorrhea. Some resistance is already being encountered in patients who are given a total dosage of 4.8 million units of penicillin, 1.2 million units in each gluteus maximus, and a similar dose in each deltoid muscle. W.H.O. has declared that the ultimate solution now appears to be immunization and has urged that research for a vaccine be given top priority.[20]

Summary

The problem of gonorrhea has been presented illustrating the factors contributing to the difficulty in control. Diagnosis by spreads poses little problem in male patients and may be used to advantage in vulvovaginitis and acute urethritis in the female. Nonspecific organisms, *Tribe mimeae*, Trichomonas, and the virus of lymphogranuloma venereum should be excluded. Cultural methods provide the most reliable aid in the asymptomatic female. A new culture medium inhibiting nonpathogenic Neisseria, *Mima polymorpha varidans*, and the bacterial flora in the vaginal and rectal tracts may prove of inestimable value. Fluorescent antibody test for the gonococcus excludes *Tribe mimeae* and is less time-consuming and more sensitive. The gonococcal complement fixation test has not been perfected.

In treatment, penicillin remains the drug of choice. Preparations which effect a high initial concentration and sustain adequate serum levels for 48 hours are preferred. A total of 2.4 to 4.8 million units of procaine penicillin in aqueous suspension given in 1 dose is recommended. Alternate antibiotics include 1 to 2 Gm. of streptomycin or 1 Gm. chloramphenicol given intramuscularly or 500 mg. of tetracycline, erythromycin, or triacetyloleandomycin 4 times a day for a total of 3 Gm. Two Gm. of Spectinomycin Sulfate given intramuscularly may be of value.

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The Treatment of Syphilis and Gonorrhea*

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Those who treated their first case of syphilis with bismuth and arsenicals, and their first case of gonorrhea with potassium permanganate and sandalwood oil can best appreciate the strides made in the treatment of these diseases in the last quarter of a century. I dare say the patients who have needed to be retreated for these diseases are even more amazed.

The first breakthrough in therapy occurred with gonorrhea in the late thirties with the advent of the sulfonamides. A short while later in the early forties penicillin revolutionized the treatment of innumerable diseases including gonorrhea and syphilis. Later, broad-spectrum antibiotics were found effective in both diseases. However, in 1966 penicillin still remains the treatment of choice in both diseases, except in those patients who are allergic to this preparation. A disquieting observation has been noted regarding gonorrhea by Dr. Thayer in our laboratory at the Venereal Disease Research Laboratory. The gonococcus has again shown an ability to develop strains that are resistant to increasing concentrations of penicillin just as it did earlier with the sulfonamides, in direct contrast to *Treponema pallidum*. So much so that in July 1965 we recommended shorter-acting penicillins that result in higher concentrations in the blood and at the same time recommended larger total dosage.

Benzathine penicillin G, procaine penicillin G with 2 per cent aluminum monostearate (PAM), or aqueous procaine penicillin G may be used intramuscularly in the treatment of any of the stages of syphilis. Oral medication is not the preferred treatment, since absorption is highly variable and patient coöperation in taking the medicine is not always obtained. When penicillin sensitivity precludes use of this drug of choice, erythromycin, tetracycline, and Declomycin® are the best alternative drugs. Recommended dosage is 20 to 30 Gm. if erythromycin or Declomycin is prescribed and 30 to 40 Gm. if tetracycline is given. Treatment should extend over a period of 10 to 15 days. If these alternate broad spectrum antibiotics are employed, very close follow-up of the syphilitic patient is necessary, since patients may not follow directions in taking their medication. Thus, it is also advisable that a spinal fluid examination be done as part of the follow-up after this type of therapy. If there is neurosyphilis the total dosage of broad spectrum antibiotics should be doubled.

Treatment of Primary and Secondary Syphilis

Benzathine penicillin G: 2.4 million units total (1.2 million units in each buttock) by intramuscular injection, or PAM: 4.8 million units total usually given 2.4 million units at first session, as above, and 1.2 million units at each of 2 subsequent injections 3 days apart, or aqueous procaine penicillin G: 600,000 units daily for 8 days to a total of 4.8 million units.

Treatment of Latent Syphilis

Benzathine penicillin G: If no spinal fluid examination is done, treatment must encompass the possibility of asymptomatic neurosyphilis. In this case, 6.0–9.0 million units total, given 3.0 million units (1.5 in each buttock each session) at 7-day intervals. With nonreactive spinal fluid examination, 2.4 million units (as primary), or PAM or aqueous procaine penicillin G as in primary syphilis.

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Treatment of Congenital Syphilis

Benzathine penicillin G: 50,000 units per Kg. of body weight at 1 clinic visit, total dosage not to exceed 5.0–6.0 million units, or aqueous procaine penicillin G: 100,000 units per Kg. of body weight divided into daily dosage over a 10-day period, total dosage not to exceed 5.0–6.0 million units.

Treatment of Late Syphilis

Benzathine penicillin G: 6.0–9.0 million units total, given 3.0 million units at 7-day intervals, or PAM: 6.0–9.0 million units total, given 1.2 million units at 3-day intervals, or aqueous procaine penicillin G: 6.0–9.0 million units total, given 600,000 units daily.

Any benefit from more than 10 million units has not been demonstrated.

Treatment of Syphilis in Pregnancy

Syphilis in pregnancy should be managed in the same manner as with any nonpregnant patient. Urgency of treatment is the keynote to therapy. If the patient is sensitive to penicillin, erythromycin should be the broad-spectrum antibiotic selected.

A question frequently raised is, "Is it necessary to retreat a woman in subsequent pregnancies or a woman who gives a history of syphilis and satisfactory treatment?" In the days of arsenical treatment (or pre-penicillin) many clinics such as that at Vanderbilt University in Nashville, Tennessee stated emphatically that "every woman with a history of syphilis must be treated during each pregnancy." Today the answer is different because of penicillin, although I find that some older physicians are carrying out the old premise of retreatment. One adequate course of penicillin treatment suffices during the life of any syphilitic patient, that is, unless reinfection or relapse occurs. This rule applies to the pregnant woman as well. It matters not whether she was adequately treated during a previous pregnancy or in a nonpregnant period. Pregnant women previously treated for syphilis should have regular physical examinations and STS at monthly intervals throughout pregnancy. If there is any doubt regarding the adequacy of previous treatment, then one should treat and with a dosage that he knows is adequate.

Preventive Treatment

If the patient is known to have been exposed to syphilis, it is a fallacy to wait for the disease to develop to the clinical or reactive serologic stage, meanwhile allowing reinfection of treated patients and the infection of additional persons. However, every effort should be made to arrive at a diagnosis, including a complete physical examination, before administering preventive treatment. Adequate preventive treatment may consist of 2.4 million units of benzathine penicillin G.

It is important to remember that in early syphilis local or generalized lesions may fail to occur or may be so slight as to escape notice, and such symptomless infection may be unsuspected until a reactive serologic test at some later time leads to the diagnosis of syphilis. Whenever undetected syphilis exists it can be spread. The resurgence of syphilis is due to progressively increasing transmission of treponemes. In order to stem this tide it is necessary to destroy the invading treponemes during the incubation period so as to prevent the onset of disease and further spread. If this destruction should take place before the primary lesion appears no transmission can occur. Preventive treatment is given for the purpose of destroying all treponemes of a contact with incubating syphilis, thus aborting the disease in its prodromal stage and rendering the patient incapable of spreading it to others.

In our field trials to determine the minimal effective treatment to abort incubating syphilis, we found that even with a field staff with considerable experience and assigned solely to this project some individuals failed to return for examination. Even with this effort a number of study participants who subsequently developed syphilis on placebo or inadequate treatment were not diagnosed until the secondary stage. Admittedly, most of the patients in whom the diagnosis was made beyond the primary stage and who were followed regularly were females, showing that primary lesions can hide beneath the vaginal speculum. It should be emphasized that if medical examination and follow-up had not been thorough the number of these embarrassing late diagnoses would undoubtedly have been higher.

The major finding of this study was that the only adequate schedule of preventive treatment tested to date was 2.4 million units of benzathine penicillin G. The study also showed that the average rate of infection following placebo was

9.2 per cent if exposure was within 3 months and 15 per cent if exposure was within 30 days prior to examination.

It was also observed in the study that an inadequate schedule of preventive treatment not only allowed the contact to develop syphilis but also resulted in the further spread of the infection to his contacts. Thus, if preventive treatment is to be an effective measure it is absolutely essential that the dosage be adequate to cure early syphilis.

Syphilis is usually related to promiscuity, and contacts frequently fall into this category. It is not reasonable to suppose that clinicians can curtail the sexual activity of these contacts while they are incubating and developing the disease during this follow-up period.

Treatment Schedules for Gonorrhea

Uncomplicated gonorrhea in men: aqueous procaine penicillin G, 2,400,000 units in 1 intramuscular injection. Uncomplicated gonorrhea in women: aqueous procaine penicillin G, 4,800,000 units intramuscularly in 2 injection sites at 1 visit, or the combination of equal parts of (1) aqueous procaine penicillin G and (2) procaine penicillin G in oil with 2 per cent aluminum monostearate for 2 separate intramuscular injections of 2,400,000 units in each site given at 1 visit.

Complications and retreatment. The treatment of gonorrhea with severe complications must be individualized with large amounts of short-acting penicillin. Excluding the likelihood of reinfection, retreatment is indicated if the discharge in uncomplicated male gonorrhea persists for 3 or more days following initial therapy and the smear, F.A., or culture is still positive. In uncomplicated gonorrhea in the female retreatment is indicated if follow-up cultures or F.A. procedures remain positive for gonococci. Retreatment consists of doubling the original dosage at a single visit or in divided doses on 2 successive days.

Penicillin sensitivity. Gonorrhea patients sensitive to penicillin may be treated effectively with tetracycline or erythromycin. These may be administered as a single oral dose of 1.5 Gm. or 0.5 Gm. given orally every 4 to 6 hours until 2 to 3 Gm. have been given.

In conclusion, let us not be discouraged by the increased rates we are seeing with these 2 diseases. Instead, let us consider how fortunate we are to have the therapeutic miracles we have in our hands today as compared to years ago and use these space-age "missiles" to wipe out these afflictions of mankind.

Chain of Venereal Disease Control—Freeman

(*Continued from page 356*)

The American Medical Association has publicly urged that every case of venereal disease be reported to the Health Department. It has stated that this does not breach the physician-patient relationship and that this coöperation by private medicine is not only desirable but obligatory.

Prenatal regulations now require a serologic test at the time of the first diagnosis of pregnancy and a second test before delivery. Hopefully, the first test will be done before the first 3½ months of pregnancy and, if syphilis is found to be present, prompt treatment will prevent infection of the infant. The effectiveness of this regulation is dependent on the coöperation of the physician.

A premarital law is most desirable. It is not believed that such a law will find many infectious cases of syphilis. However, the requirement of a serologic test for syphilis before issuance of a marriage license will alert the partners, if the test is positive, that treatment is indicated. Such treatment may prevent the late sequelae of the disease. Additionally, the knowledge that the wife has a positive serologic test for syphilis will assure that, in the event pregnancy ensues, prompt therapy will prevent syphilis in the offspring. Compulsory laboratory reporting of positive serologic reactors has made it possible to follow many hitherto unknown patients.

In conclusion, a venereal disease control program must be formed by a chain, each link of which must be as strong as it can be forged. Weakness of any link weakens the chain. Case-finding, clinic facilities, education, Health Department services, and legal aids are 5 links which, if individually well planned and strong, will form a sturdy chain of venereal disease control.

New Developments in Venereal Disease Research*

JAMES B. LUCAS, M.D.†

WITH THE RECRUDESCENCE of the venereal diseases on a world-wide basis there is occurring a renaissance of scientific interest in venereal disease research. Many investigators throughout the world are once again turning to the manifold problems presented by syphilis and gonorrhea. In the last decade it has become obvious that antibiotic therapy, once thought to be the complete solution to the venereal disease problem, will not alone suffice in bringing control to these diseases.

Significant advances, both in the serologic diagnosis of syphilis and in the detection of gonorrhea, have spearheaded recent scientific advances. Other challenging problem areas currently under study include epidemiology, the evaluation of new drugs, the problem of prophylaxis, and further refinements in diagnostic techniques. The whole problem of immunity in both syphilis and gonorrhea, with possible applications related to vaccine development, needs reëvaluation in the light of the currently burgeoning new knowledges and tools made available by the achievements of modern immunology.

Syphilis

One of the most exciting developments stemming from research at the Venereal Disease Research Laboratory has been the fluorescent treponemal antibody–absorption test or FTA-ABs test.[1] This test is now fully operational, culminating 10 years of research in this area of syphilis serology. The absorbed FA test appears to be a logical successor to the Reiter protein complement-fixation (RPCF) test and the FTA-200 in the assessment of clinical "problem" cases or suspected biologic false positives.

The FTA-ABs has far greater sensitivity than either the RPCF or FTA-200 while retaining the specificity offered by these procedures. While definitive comparisons of the FTA-ABs with other standard tests for syphilis still await publication, ample data have been collected from centers in coöperation with VDRL to justify earlier expectations.[2] Table 1 shows the relative reactivity of VDRL, TPI, and FTA-ABs in the various stages of syphilis. Note the quite high rate of reactors obtained with the FTA-ABs test in primary syphilis compared with the TPI. Also notice that in all categories of patients the FTA-ABs equals or betters the classical TPI procedure.

TABLE 1: Reactivity of VDRL, TPI and FTA-ABs in the Stages of Syphilis

	Primary Syphilis	Secondary Syphilis	Latent Syphilis	Late Congenital and Symptomatic Syphilis
VDRL slide	77%	97%	75%	75%
TPI	56%	94%	82%	93%
FTA-ABs	85%	99%	95%	96%
Total Cases	191	267	892	114

Table 2 shows the results of TPI and FTA-ABs testing in control "normals" and patients originally diagnosed as having BFP. Note that there is no disagreement between the 2 tests for the 307 "normals." Five of this group appear to have actually had a treponemal infection despite a negative clinical picture, history, and screening VDRL slide test. The lower half of the table indicates the comparative behavior of the 2 tests with sera from 502 patients originally thought to be BFP's. Notice that 239, or nearly half, appear to have had a syphilitic infection. This corresponds to previous studies which have shown that actually about one-half of clinically diagnosed BFP's indeed have or have had syphilis.[3] Note carefully the 2 categories in which the tests disagree, i.e., the serum being positive in only one test or the other. Since it has been shown that the FTA-ABs test is the more sensitive procedure in clinically definable categories of syphilis, it is a logical assumption that the same holds true in the BFP "problem patient" as well.

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TABLE 2: Results of TPI and FTA-ABs Testing in Control "Normals" and Patients Originally Diagnosed as Having BFP Reactions

Normal controls	307
TPI and FTA-ABs negative	302
TPI and FTA-ABs reactive	5
BFP cases	502
TPI and FTA-ABs negative	216
TPI and FTA-ABs reactive	239
TPI negative and FTA-ABs reactive	31
TPI reactive and FTA-ABs negative	16

Based on these and other studies it appears that the FTA-ABs test is as highly specific as the TPI but more sensitive, particularly in early or late cases in which the amount of antibody present can be expected to be minimal.

The FTA-ABs is rapid, inexpensive, readily reproducible, and lends itself well even to laboratories having comparatively small volumes of serologic tests. Any laboratory with experience and competence in fluorescent microscopy should have little difficulty or expense in adopting this procedure. We fully expect that the FTA-ABs test will supplant the TPI examination in nearly every clinical situation requiring this type of serological investigation within the next few years. The TPI will probably be reserved for those rare situations in which the FTA-ABs is nonreactive and in those unusual instances in which a significant element of doubt concerning the diagnosis continues to persist. Reagents for the FTA-ABs test are currently available from Difco Laboratories, Detroit, Michigan, and other commercial companies are expected to begin production in the near future.

Gonorrhea

The last 5 or 6 years have witnessed a revolution in the diagnosis of gonorrhea. Nonetheless, the Gram stain, after 60 years, still remains one of the most frequently used tools. While usually quite satisfactory in acute, uncomplicated, gonococcal urethritis in males it is of very limited value in the asymptomatic male or female.

Cultural identification so essential to the diagnosis of gonorrhea in the female was once an arduous, painstaking procedure which could be carried on only in the most sophisticated laboratories. The identification of *Neisseria gonorrhoeae* has been greatly simplified by the introduction of 2 new basic techniques.

Deacon[4] in 1959 developed the first of these new tools by applying fluorescent antibody procedures to the problem of *Neisseria gonorrhoeae* identification. With this new application the following diagnostic tests were developed: immediate direct FA, delayed direct FA, and rapid immunofluorescent staining.

In diagnosing acute gonorrhea in males any of the 3 FA methods is equal to the culture or Gram's stain in sensitivity. However, at least in diagnostic situations, the FA procedures are virtually specific for *N. gonorrhoeae* and are thus preferable to Gram's stain.

In asymptomatic female contacts, in whom the number of organisms present is frequently few, the immediate direct FA procedure will be positive in only 25 to 35 per cent of cases. By culturing negative specimens for 16 hours and then performing the direct FA procedure the positivity rate is increased to approximately 50 to 60 per cent. The additional culture increases the number of organisms and thereby the sensitivity.

In 1964 Kellogg[5] developed the rapid immunofluorescent staining procedure which requires only about a minute to perform. This procedure was found to be as sensitive as the immediate direct FA test if the same conjugate was utilized. This test is in need of further evaluation.

One major problem in FA diagnosis is background fluorescence. It has been aptly stated that all that glitters is not gold, and all that fluoresces is not *N. gonorrhoeae*. To read the FA test one must be carefully trained to identify only the typical fluorescing diplococcal form of the gonococcus. To help eliminate the problem of fluorescing artifacts it has been suggested that flazo-orange[6] or Evans blue dye[7] be added to the staining procedure. These dyes, acting as counterstains, stain white cells, other bacteria, and artifacts which frequently confuse the microscopist. These refinements help reduce the rather lengthy examinations required when only occasional organisms are present on the preparation.

In 1964 Thayer and Martin[8] reported a culture medium selective for the pathogenic *Neisseria.* This remarkable achievement, coming as it has on the heels of FA techniques, has tended to decrease interest in these tools. In a scant 2 years since its introduction the Thayer-Martin medium has gained wide acceptance. When typical colonial morphology, the oxidase reaction, and the characteristic Gram stain reaction are in agreement for colonies grown on T-M media, the presumptive diagnosis of *N. gonorrhoeae* is virtually equivalent to definitive diagnosis which requires secondary sugar fermentation reactions. Naturally, should the presumptive diagnosis be suspect or should the case have possible medicolegal overtones, sugar fermentation studies must be employed. Reports from England and elsewhere have amply confirmed the value of this diagnostic procedure.[9] The results obtained on T-M medium when specimens are taken from heavily contaminated sites such as the vagina or rectum far surpass the best performance of conventional media. It has come as something of a surprise to find that the diagnostic results even with specimens from relatively uncontaminated sites, for example, the male urethra, also show significantly higher rates of isolation.

Soon after the development of the original Thayer-Martin medium, which contains ristocetin and polymyxin B in a final concentration of 25 units and 10 mcg. per ml. of medium, Abbott Laboratories, the sole manufacturer of ristocetin, announced that they planned to discontinue manufacture of this antibiotic. This dilemma was solved by the development of a new antibiotic supplement containing 3 units of vancomycin, 7.5 mcg. of sodium colistin, and 12.5 units of nystatin per ml. The latter antibiotic was added to reduce the incidence of yeasts recovered from vaginal or rectal cultures. This new "T-M" or "VCN" medium, as it is known, has proven to be actually superior to the original antibiotic formulation allowing an even greater diagnostic yield.[10] This antibiotic combination is less inhibitory to the gonococcus than was the old ristocetin-polymyxin supplement while inhibiting a wider range of saprophytic organisms.

Recently a new commercial supplementary enrichment useful for the primary isolation of *N. gonorrhoeae* has been developed by Baltimore Biologic Laboratories. This supplement, named Isovitalex, differs from others normally added to chocolate media in that the added enrichment, instead of being a biological or yeast extract, is chemically defined. When this supplement is combined with the VCN antibiotics nearly twice the actual number of gonococcal colonies are recovered (489 compared with 253 for media without the defined supplement but containing the VCN antibiotics).[11] Moreover, identifiable colonial growths of gonococci are almost always present after only 16 hours of incubation instead of the normal 24 hours or more usually required. It is also of importance to note that this new combination is as useful in detecting meningococci as the original T-M medium.

This development indicates that cultural methods can now compete favorably on a time basis with the 18-hour delayed fluorescent antibody technique while maintaining the objectivity and increased sensitivity inherent in cultural methods. Although the delayed FA procedure remains a useful tool in some instances it has for all practical purposes been supplanted in the diagnostic laboratory by the improved cultural methods currently available. Studies have shown that the cultural method is 10 to 15 per cent more sensitive in detecting the gonococcus.[12] Further advantages include speed, ease, and economy. New technicians can become competent with only a few hours' training, and highly skilled personnel are freed for other duties. The problem of preparing an entirely specific fluorescent conjugate has not been overcome despite absorption with various microörganisms and the addition of whole human serum.

Nonspecific staining of certain strains of staphylococci is particularly distressing following antibiotic therapy. It was early recognized that dead organisms, i.e., gonococci, would stain as long as they remained present following therapy and that the FA procedure could not be used as a test of cure for the first few days immediately following treatment. However, it has only recently been noted that false-positive FA results may persist for much longer periods following therapy. The mechanism apparently involved concerns the increase in the normally minimal numbers of penicillin-resistant staphylococci which follow the use of all types of antibiotics. These FA-positive organisms which persist beyond the duration of the use of an antibiotic diminish as the normal flora of the body becomes reëstablished. Hence, if long-acting penicillin preparations have been used, this source of error in the FA test may persist for several weeks or even longer.

The problem of lessened susceptibility to penicillin by certain strains of gonococci is becoming a matter of national concern. This relative "resistance" to penicillin was little more than a laboratory curiosity less than 10 years ago. In this interval escalated penicillin dosages have become necessary to cure patients with gonorrhea.

In a recent Nation-wide survey of this problem it was noted that considerable geographic variations existed.[2] Some cities exhibit only occasional strains of gonococci requiring 0.5 μ/ml. of penicillin for in vitro inhibition, while such strains are commonplace in other areas. Due to mobility of people there is no doubt that these more resistant strains will become widely disseminated.

When infection is caused by a "resistant" strain high penicillin blood levels are required for cure. To achieve these prerequisite blood levels, short-acting penicillins must be employed. Hence, along with increasing dosages there has also been an accompanying shift to short-acting penicillin preparations. Most authorities feel that the formerly widespread practice of treating gonorrhea with long-acting penicillin has actually contributed to the loss of gonococcal sensitivity. Certainly, reinfection in the presence of long-lasting subinhibitory levels of penicillin cannot have had a beneficial effect. It must be remembered that the use of such preparations in the guise of preventing reinfection or as an antibiotic quarantine is a false premise, since reinfection is actually only delayed and not prevented.

Fortunately, to date, antibiotic resistance in gonorrhea has developed slowly and in a stepwise manner. However, the trend toward resistance appears to be increasing steadily, and the problem of evaluating the many new antibiotics for effectiveness in gonorrhea becomes increasingly pressing and challenging.

Because of the high asymptomatic carrier rate of females with gonorrhea it is generally agreed that a serologic test readily applicable to large-scale detection of the disease would be a valuable adjunct in the control of this continuing public health problem. Although the present diagnostic methods are relatively accurate and reliable they are only applicable to patients who present themselves for diagnosis and treatment. The vast asymptomatic female reservoir is unaffected by present control measures. A serologic test which might be applied in the same manner as the serologic tests for syphilis, perhaps even on an aliquot of the same serum specimen, would represent real progress in gonorrhea control. Much effort to evolve a successful serologic test for gonorrhea is currently being expended at the Venereal Disease Research Laboratory. Serologic tests for gonorrhea are not new; for example, the complement-fixation reaction with gonococcal antigen has been known for nearly as long as the Wassermann reaction. In the years preceding World War II the gonococcal C.F. test was widely employed both in this country and throughout Europe. Interest in this procedure has diminished in the intervening years except for the occasional reports of a few investigators. The demise of this procedure can for all practical purposes be considered complete, at least within the United States. An apparent lack of specificity, combined with improvements in cultural methods of diagnosis, has been the major factor responsible for this situation. However, interest in the complement-fixation technique and the application of other immunological testing procedures to the gonorrhea problem has been rekindled in the past several years.

The evaluation of investigations in this field which are not carried out by identical techniques is extremely difficult. It must be remembered that by working with different amounts of reagents and serum the sensitivity of the reaction is influenced. Different antigens also will elicit different degrees of reactivity. In general, as with serologic tests for syphilis, it can be stated that, as sensitivity increases, specificity diminishes.

A new test for the detection of gonococcal antibody has been developed by Reising and Kellogg.[13] These workers employ a phenol-extractable antigen in a microprecipitin test. This antigen appears to be highly specific, and no crossing with meningococcal strains has been noted. Nonreactive results were obtained with all 73 sera obtained from persons without a history or physical evidence of gonorrhea. Seventy-three per cent of male gonorrhea patients and 60 per cent of females with culturally or FA-proven gonorrhea were reactive in this test procedure. These results compare favorably with those obtained with the C.F. test recently reported by Magnusson and Kjellander.[14] These workers found positive reactions in 37 per cent of males and 53 per cent of females. A large control group indicated a high degree of specificity for their procedure since only 1 per cent of

(*Continued on page 404*)

PRESIDENT'S PAGE

MEDICAL LICENSURE IN THE DISTRICT OF COLUMBIA

Inasmuch as Washington, D. C. has in recent years become one of the crossroads of the world, the requirements and problems related to medical licensure in the District of Columbia have become extremely involved. Many of the current applicants have received their medical education in foreign schools while many others who had been in the military or other governmental service seek licensure on the basis of reciprocity.

The existing licensing mechanism which has been in operation for many years is, in my opinion, antiquated and inadequate. It obviously needs updating, both from the standpoint of the medical examination technique and also the application of reciprocity rulings.

The Medical Society of the District of Columbia has a clear responsibility in this area, in response to which an ad hoc committee, chairmaned by Dr. John Hughes, has been appointed to study the problem in depth and to recommend any necessary changes. One reasonable suggestion is that the Medical Society should have a voice in the selection of the members of the Board of Medical Examiners. Other suggestions from members of the Society are earnestly solicited by Dr. Hughes and his committee.

in diarrhea

LOMOTIL® Tablets / Liquid

Each tablet and each 5 cc. of liquid contains:
diphenoxylate hydrochloride . . . . 2.5 mg.
(Warning: May be habit forming)
atropine sulfate . . . . 0.025 mg.

is a corker

Effectiveness: Lomotil possesses a unique degree of effectiveness in both acute and chronic diarrhea.

Convenience: Lomotil is supplied as small, easily carried, easily swallowed tablets and as a pleasant, fruit-flavored liquid.

Versatility: The therapeutic efficiency, safety and convenience of Lomotil may be used to advantage alone or as adjunctive therapy in diarrhea associated with:

- **Ulcerative colitis**
- **Acute infections**
- **Irritable bowel**
- **Regional enteritis**
- **Drug therapy**
- **Food Poisoning**
- **Functional hypermotility**
- **Malabsorption syndrome**
- **Ileostomy**
- **Gastroenteritis and colitis**

Dosage: For full therapeutic effect—Rx full therapeutic dosage. The recommended initial daily dosages, given in divided doses, until diarrhea is controlled, are:

Children: 3 to 6 months — 3 mg. (½ tsp.* t.i.d.)
6 to 12 months — 4 mg. (½ tsp. q.i.d.)
1 to 2 years — 5 mg. (½ tsp. 5 times daily)
2 to 5 years — 6 mg. (1 tsp. t.i.d.)
5 to 8 years — 8 mg. (1 tsp. q.i.d.)
8 to 12 years —10 mg. (1 tsp. 5 times daily)
Adults: 20 mg. (2 tsp. 5 times daily or 2 tablets 4 times daily)
*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the therapeutic dose.

Precautions: Lomotil, brand of diphenoxylate hydrochloride with atropine sulfate, is a Federally exempt narcotic preparation of very low addictive potential. Recommended dosages should not be exceeded. Lomotil should be used with caution in patients with impaired liver function and in patients taking addicting drugs or barbiturates. The subtherapeutic amount of atropine is added to discourage deliberate overdosage.

Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness, insomnia, numbness of extremities, headache, blurring of vision, swelling of the gums, euphoria, depression and general malaise.

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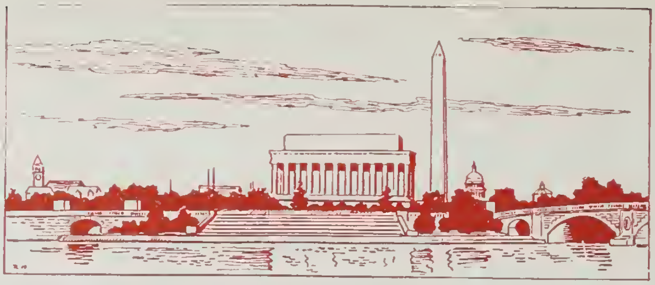

EDITORIALS

Physician's Responsibility in Venereal Disease Control

The private physician holds the key to syphilis control. A recent study indicated that more than half of the patients diagnosed as primary or secondary syphilis are being treated by private physicians, and few of these cases are being reported or epidemiologically investigated.

To accomplish control and eventual eradication of venereal disease there must be complete alliance between the private physician and Public Health. Without an intensive, coöperative and aggressive attitude toward these diseases, our goal of eradication cannot be attained. Even with all medical forces pulling together the task is still a difficult one. We must concern ourselves with lack of health education, with an increasingly mobile population, with greater freedom of the teen-agers, with the homosexual, and with urbanization of the population. We must remain alert that we do not err again, as we did in 1957, when the rate of new infections reached the lowest point in our history. With this success came complacency. Congress reduced venereal disease budgets to a minimum; medical staffs were reduced or eliminated; education was abandoned; contact investigations ceased; and the medical profession lessened its concern with this problem.

By 1958 the rate was climbing, until by 1964 the rate was $3\frac{1}{2}$ times that of 1957. We must not repeat this failure in this fight for eradication. As all the forces of medicine are arrayed to do battle with this enemy, let us remember that as the rate of infection drops our efforts at case-finding must be intensified. A sustained, coördinated and relentless attack must be waged. Treatment of the infected syphilitic at the very earliest period of his infection is most essential, but equally as important is the finding of every source and spread contact of that patient in order to determine if they are infected. This can only be done if the private practitioner will face up to his legal and medical responsibility in reporting each case of syphilis to the health authorities and giving permission to have his patient interviewed. Do not be deluded into thinking that the responsibility of the private physician reporting and coöperating in permitting epidemiological follow-up is without its problems. Tremendous pressure is exerted by prominent patients who may have contracted syphilis to influence the physician and make certain that his case is not reported. It requires a dedicated physician to overcome these objections and report such a case. The physician fears loss of his patient and a possible breach of the physician-patient relationship. The patient suffers from fear, remorse, shame, and the consequence of exposure of an illicit relationship. All of these must be dispelled, and the patient and the physician must receive assurance of the complete confidentiality of the epidemiologic inquiry.

The District of Columbia for the past 3 years has shown a continued decline in reported cases of infectious syphilis. In fiscal year 1963 there were 711 cases of infectious syphilis; in fiscal 1964, 576 cases; in fiscal 1965, 551; and on the basis of the first 6 months of fiscal 1966 we expect 488 cases in the present year. This decreasing incidence, as encouraging as it is, must not signal a lessened effort but, rather, increased diligence to ferret out every case of syphilis in the District of Columbia.

There must be no lapse in effort, no pause in the relentless search for the elusive spirochete. A continued, sustained and persistent search must be aggressively launched to find and destroy this enemy of mankind. Only if private medicine and Public Health join forces and work in harmony and with dedication can we hope to achieve control and eventual eradication of syphilis.

C. Wendell Freeman, M.D.
Chief, Venereal Disease Control Division,
D. C. Department of Public Health

Opinions expressed in contributions to the Editorial Section are those of the writers and do not necessarily reflect the views of the Medical Society of the District of Columbia

The "Grass Roots" Voice—Pro and Con

The Bulletin of the Los Angeles County Medical Association recently (March 17, 1966) published an abstract from a speech by Dr. Edward R. Annis, Past President of the American Medical Association, which lauded and supported the newly formed Congress of County Medical Societies.

Perhaps I could agree with Dr. Annis if this Congress were an integral part of AMA, but another "splinter" in medical organization is not needed today. Actually, such "splinters" were not needed when a number of national medical groups were formed this past 20 years. They have served to confuse rather than fuse medicine.

About 20 years ago the AMA recognized the need of an exchange of county society viewpoints and established a "Grass Roots Conference." This annual affair attracted 400 to 500 doctors from the "grass roots"—the county medical societies. Eventually it was supplanted by the Conference of State Medical Society Officers.

The Grass Roots Conferences were free-swinging meetings devoted to real controversial subjects, but they were under AMA aegis. The Academy of General Practice was the result of such a meeting held in Cleveland. A review of these meetings would reveal other lasting results.

If there is to be a revival of the "grass roots" voice, and I heartily agree it could be beneficial, such a revival should be under AMA auspices and not an independent "Congress." The former as a forum for discussion would strengthen medicine; the latter, as a "splinter" group, will weaken medicine and soon be in conflict with the AMA House of Delegates.

G. C.

Medicare Prepares to Function

On July 1 the so-called Medicare Law (P.L. 89-97) became effective.

A Medicare Reference Guide with information on what the new program of health insurance for the aged provides and how it will work has been mailed to the Nation's 280,000 physicians, according to Mr. Robert M. Ball, Commissioner of Social Security.

Developed with the assistance of the American Medical Association and other organizations in the health care field, the Reference Guide for physicians describes the benefits payable for the Nation's elderly people under the hospital insurance program and the payments for doctor bills and other medical services under the voluntary program of medical insurance in which 9 out of 10 of those 65 and over have enrolled.

Under Part A of P.L. 89–97 (hospitalization) doctors should review carefully each eligible case he hospitalizes, both before entry and during the hospital stay. The Society's Hospital Utilization Review Committee, composed of representatives from each individual hospital's Utilization Review Committee, has prepared guidelines for these committees.

Under Part B (physicians' services) Medical Service of D. C. is the administrative agent. A "Request for Payment" form will be used for claims under this part of the program. Those over 65 who have enrolled for Part B will be eligible for 80 per cent of their doctor bills and other medical expenses after they have met the first $50 of these expenses.

Two methods of billing are available to physicians:

Under the first method the doctor will bill the patient, and after the patient has paid the bill, he will claim reimbursement on the "Request for Payment" form and attach the doctor's itemized bills. The physician will need to fill out the bottom half of this form only if the itemized bills do not provide the necessary basic facts as to services and when and where they were performed. Under this method the physician's charges will be between him and the patient; what the patient receives as reimbursement will be between him and the administrative agent.

Under the second method the patient fills out the top half of the "Request for Payment" form and gives it to the doctor. The doctor will complete the bottom half and forward the form to the administrative agent for payment. With this method the doctor agrees to accept the amount paid him by the administrative agent as 80 per cent of his total bill over and above the $50 deductible and agrees to collect no more than the remaining 20 per cent from the patient, plus any part of the $50 deductible still owing.

The above does not necessarily apply to payment to pathologists and radiologists who are compensated by or through a hospital. They will have a special and more complicated billing procedure.

Along with his Reference Guide each physician has been mailed an advance copy of "Your Medicare Handbook" that was sent during the month of June to the 19.1 million people 65 and over who are covered by the Medicare program. Physicians should urge any of their patients so covered to read this booklet carefully.

R_x for Art Lovers

A PROMINENT CALIFORNIA FINANCIER and art patron, Bert Lytton, told 400 members of the Santa Clara Medical Society and their wives at a meeting last fall that physicians ought to take a critical diagnostic look at the physical adornment and decor of their waiting rooms, hospitals, and other medical service areas.

"I remember the dreary waiting rooms of my childhood when *The National Geographic* and perhaps an old *Literary Digest* provided the only break from sterile decor and wall treatment, coldly relieved by a colorless array of diplomas, licenses, and credentials," Lytton recalled.

"Dress up your office," he advised the doctors. "You'll like it better, your nurse and assistants will like it better, and your patients will be eternally grateful."

Calling on his own extensive experience in acquiring the widely-known Lytton collection, the financier offered these special guidelines for physicians initiating an art acquisition program:

(a) Give consideration to contemporary—preferably regional—art but avoid entirely the macabre; it's deadly.

(b) Avoid anything reminiscent of illness or death as a theme.

(c) Seek cheerful, bright colors and pleasing forms, and avoid dark, sombre or blood colors and involved, intricate or tortured forms.

In addition to undertaking acquisition and display of fine works of art in their own offices, physicians were urged by the financier to use their influence in extending the attitude into hospitals and other medical service facilities with which they are associated.

Besides the practical immediate benefits that come through having tastefully decorated offices and public facilities, Lytton said physicians and their wives who enter the field of buying original works of art will soon find a sense of fun and discovery which will accompany them throughout their lives, adding enjoyment and dimension to daily living.

"It's easy enough to lean on the past and the tried and traditional in art, to buy reproductions and even an occasional recognized master when such acquisition can be undertaken," he said. "Art museums preserve the past to give us better understanding of the present. Our principal challenge, however, is the present—to build the future better. It is the living artist—contemporary, even regional—who warrants our main support. . . .

"Enjoyment comes when a painting or sculpture you bought a number of years ago from a relatively unknown artist begins to gain stature as the artist is recognized for his genius and achievement. The feeling that you were among the original small group which recognized the talent the artist evidences gives the 'game' of collecting a distinctive sense of joy."

From an investment standpoint, Lytton pointed out, acquisition of reasonably well-chosen art has proven worthwhile over the years. Competently chosen works of art tend to increase in value, he said. Such additions to offices or other medical facilities are, generally, not permanent attachments and can be moved or replaced.

He urged the acquisition of art be handled much like building a savings account, through periodic additions as they can be comfortably financed by the physician.

For those who feel unsure of the first step, Lytton suggested consulting a "specialist." Get acquainted with a number of established galleries in your own and nearby communities. Depend on them for advice. Don't hesitate to go back again and again with questions.

You can trust established galleries and dealers. Their continued success as a business institution relates closely to the continued confidence of their customers. They are the trained experts and they have a world of information, advice, and suggestions to offer you for nothing, holding the hope, of course, that you will become a regular customer.—*From a News Release, October 18, 1965, by Lytton Financial Corporation, Los Angeles, Calif.*

Annual Report of President of Medical Service*

THIS IS MY FINAL MESSAGE to you as President of Medical Service of the District of Columbia. I would be less than candid if I did not tell you that in relinquishing my office I have mixed feelings. First is my regret that I shall no longer be a member of Medical Service's Board of Trustees which, in my opinion, is doing such a splendid job in furthering the best interests of the public and the medical profession in a rapidly changing world. My association with such a fine group of dedicated men has meant a great deal to me. On the other hand, it will be of some comfort not to be burdened with an office naturally and frequently subject to censure and reproach, which often entails more frustrations than the actual hours of toil. Nevertheless, I can honestly say I have found my tenure as President an enlightening, stimulating, and a pleasant experience.

Medical Service's Progress

At the beginning of my presidency in 1961 there were 828,000 individuals enrolled in Medical Service. As of March 30, 1966, there were 1,044,000. This growth has been most gratifying to me and I know it is to all who are concerned with the success of our Plan. However, a note of caution as to the rapidity of growth in the future should be injected here.

As I pointed out to you in my report last year, many groups and individuals have resisted substantial increases in subscription rates. They demand greater coverage but are reluctant to pay the additional cost. Dissatisfaction has also been expressed by Participating Physicians with certain categories of physicians' fees. Throughout the year innumerable conferences have been held in an attempt to reach mutually satisfactory conclusions with respect to fees. Increases which will become effective July 1 should ameliorate this situation to a considerable degree. But this has been and will always be a continuing problem.

To refresh your memory in regard to changes which will become effective July 1, I shall review them briefly.

Under the Extended Surgical-Medical Contract, fee schedule allowances will be accepted as full payment by Participating Physicians for services rendered under the Plan if the subscriber is a single participant and his income does not exceed $5,000 a year, or if he is a family participant and his total family income does not exceed $7,500 a year. Fee schedule allowances payable for surgical procedures and administration of anesthetics will be increased with the new schedule, providing allowances ranging up to $495 for a single surgical procedure. The highest fee schedule allowance payable for a single procedure was formerly $300. Fees for in-hospital medical services will be increased 20 per cent by reason of higher conversion factors for medical services which are applicable to the higher income levels which will be in effect for this contract.

Surgical and Surgical-Medical Contract income levels will remain $4,000 for the single participant and $6,000 for the family participant. Fee schedule allowances payable for surgical procedures and administration of anesthetics will be increased with the new schedule, providing allowances up to $412 for a single procedure. The highest fee schedule amount payable for a single procedure was formerly $300.

Benefits for consultations and intensive care for 11 days, beginning with the fourth day of hospitalization, will be included under the Surgical-Medical Contract.

In an effort to update benefit provisions of Basic Medical Service Contracts, the following changes were adopted by the Executive Committee and approved by the Board of Trustees:

- That benefits for physician visits in approved mental hospitals be provided for a maximum of 27 visits under the Surgical-Medical Contract and 30 visits under the Extended Surgical-Medical Contract during a continuous period of hospitalization up to 30 days. Formerly no benefits were offered for in-hospital medical visits in a mental hospital.
- That the exclusion of congenital anomalies be removed from the Surgical Contract. These benefits formerly were provided under this contract only for children born after the effective date of family coverage.
- That the age for participation of dependent children be reduced to 14 days under the Surgical Contract. It was formerly 90 days.
- That the age for participation be reduced to the day of birth for dependent children under basic coverage, when such coverage is part of the comprehensive program. Formerly, dependent children enrolled under the comprehensive coverage were protected from birth only under the major medical segment of the comprehensive program.

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* Presented at the Annual Meeting of Participating Physicians of Medical Service of the District of Columbia, May 25, 1966.

New
low-cost tetracycline/antifungal therapy

for broad-spectrum activity
plus specific antifungal prophylaxis
at significant patient savings

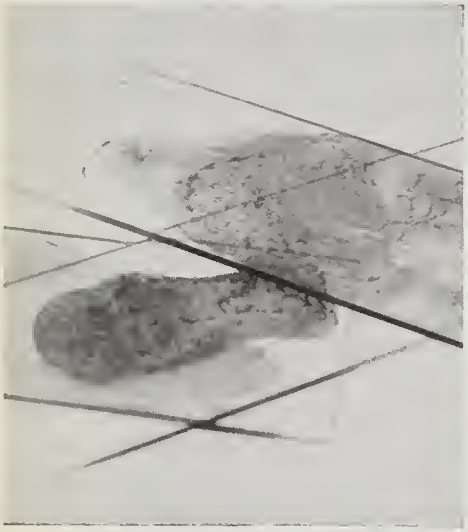
Whenever tetracycline is indicated in these candidates for Candida

1. diabetic patients

2. nonpregnant women with a history of recent or recurrent monilial vaginitis

3. elderly or debilitated patients

4. patients with a past history of moniliasis



5. patients on long-term tetracycline or corticosteroid therapy

BRISTOL THERAPEUTIC SUMMARY: For complete
formation consult Official Package Circular. *Indicati*
Infections of respiratory, gastrointestinal and genitouri
tracts and skin and soft tissues due to tetracycline-s
tive organisms, in patients with increased susceptib
to monilial infections. *Contraindications:* The drug is
traindicated in patients hypersensitive to its compon
Warnings: Photodynamic reactions have been produce
tetracyclines. Natural and artificial sunlight should
avoided during therapy. Stop treatment if skin discon
occurs. No cases of photosensitivity have been repo
with Tetrex (tetracycline phosphate complex). With
impairment, systemic accumulation and hepatotoxicity
occur. In this situation, lower doses should be used. T
staining and enamel hypoplasia may be induced du
tooth development (last trimester of pregnancy, neon
period and childhood). *Precautions:* Bacterial superin
tion may occur. Infants may develop increased intracra
pressure with bulging fontanels. In gonorrheal ther
serologic tests for syphilis should be conducted init
and monthly for 3 months. *Adverse Reactions:* Glos
stomatitis, nausea, diarrhea, flatulence, proctitis, vagin
dermatitis, and allergic reactions may occur. *Usual A*
Dosage: 1 capsule *q.i.d.* Continue therapy for 10 day
beta-hemolytic streptococcal infections. Administer
hour before or 2 hours after meals. *Supply:* Capsules,
tles of 16. Each capsule contains tetracycline phosp
complex equivalent to 250 mg. tetracycline HCl acti
and 250,000 units of nystatin.

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BRISTOL LABORATORIES
Division of Bristol-Myers Company
Syracuse, New York

Tetrex-F®

Each capsule contains tetracycline phosphate complex equivalent to tetracycline hydrochloride 250 mg. and nystatin 250,000 unit

Tetrex-F is priced lower
than most
tetracycline-antifungal products.

- And finally, that unmarried dependent children who are 19 years of age or older may continue under the family coverage if they are incapable of self-sustaining employment by reason of mental retardation or physical handicap, and if such condition occurred prior to age 19. This is a new benefit.

Incidentally, these changes are listed in the May issue of *The Reporter*, which I hope you file each month for reference purposes.

Medicare

Medical Service of D. C., at the request of its Board of Trustees, was designated the carrier for the Washington Metropolitan Area for Part B, Title XVIII, the Medical Insurance Program of Medicare. In making its request the Board had no illusions about the problems inherent in this program. In the role of liaison between physicians and the Government, it expects to find itself in the middle of many unforeseen complications. Nevertheless, Medicare is now law and your Board believes most of you will agree that it is highly desirable that it be administered by a voluntary organization, especially one in which the medical profession has a voice.

Although my responsibilities as your President will terminate before Medicare is well under way, my plea to Participating Physicians is that they coöperate with Medical Service in this new venture, thereby demonstrating their confidence in the voluntary prepayment plan of which the Medical Society of D. C. was the sponsor.

Blue Cross 65 and Blue Shield 65

On March 22, 1966, Mr. F. P. Rawlings, Jr., President of Group Hospitalization, Inc. and I, as President of Medical Service of D. C., issued the following joint statement announcing new programs for senior citizens entitled to the benefits under Medicare:

"These programs have been developed for persons 65 or more years of age to meet some of the health care expenses Medicare will not cover. The Blue Cross 65 and Blue Shield 65 programs will complement but not duplicate the protection offered by Part A and Part B of Medicare. The benefits together with those offered by Medicare provide a well-rounded program of health protection for the over-65 age group."

Blue Shield 65 will pay the first $50 and 20 per cent of the balance of an amount up to the "reasonable charge" as determined under Medicare for physicians' services each calendar year (except home and office visits). These services include surgery, administration of anesthetics, in-hospital medical visits to hospitalized bed patients (including intensive care visits and consultations), diagnostic laboratory and radiological procedures, endoscopies, electroshock therapy, radiation and isotope therapy, and emergency first-aid service.

Blue Cross, on the other hand, will pay the first $40 of hospital charges, $10 a day toward the hospital charges beginning with the 61st and ending with the 90th day, the cost of hospital care beginning the 91st day to the 180th day, the cost of hospital care beginning with the first day to the 180th day for services rendered outside the United States and Its Possessions.

Several calls have been received inquiring when the present over-65 subscribers to Medical Service will receive applications for this coverage. They have been mailed.

Adoption of the PSI as the Relative Value Scale for Medical Service and Increase in Conversion Factors

In a letter directed to Participating Physicians dated June 10, 1965 the Board of Trustees proposed that the Professional Services Index (PSI) be adopted for use with local contracts and programs as well as for the Senior Citizen Contract (which, when Medicare becomes effective July 1, will be discontinued), the Federal Employee Program, and national accounts. It was recommended that conversion factors for surgery, delivery and anesthesia be increased by 11 per cent. Those in effect for in-hospital medical services and diagnostic examinations would remain unchanged. The fee schedule for laboratory and radiological procedures now in use for both local and national accounts would continue to be used. The response was gratifyingly large, all but a small minority voting in favor of the foregoing proposals.

Educational Program

As in the past, every effort has been made to inform Participating Physicians about Medical Service—its policies, administration and operation. Means by which this is being done at present are:

A Handbook for Participating Physicians. Each of you have, or at least should have, a copy of the Handbook, because it has been mailed to every Participating Physician. If you will devote only a half hour or so to familiarize yourself with its contents, or at least have your office assistant do so, you will be well rewarded. It contains, in

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condensed form, essential information about Medical Service—schedule of fees, contract guide, and by-laws.

Changes which will become effective July 1 require a revision of the schedule of fees and the contract guide. Pages containing these changes will soon be made available to you.

I should like to emphasize the value of the contract guide. If you use it consistently it will save you and your office assistants much time. This is especially true when subscribers to Medical Service who come to your office are unfamiliar with the benefits to which they are entitled. Using the guide you can provide them with this information in a matter of minutes.

Practical Demonstrations for Doctors' Office Assistants. The demonstrations continue to be very helpful and attractive to doctors' office assistants. Since they were initiated in January, 1964, 682 have attended. Each demonstration was limited to 25 participants so as to provide ample opportunity for those present to ask questions. Subjects discussed have been the use of the contract guide, how to determine fees for a given procedure, how to complete a basic claim form (Physician's Service Report), and an explanation of the Major Medical and Supplemental benefits.

The Reporter. You have long since become familiar with this publication. It has been purposely kept modest in size and readable. As you have discovered, its contents are limited, with very few exceptions, to educational material.

These are just a few of the things being done in this area. A new program will soon be announced entitled "Medicare in the Washington Metropolitan Area." This will be a practical and instructive type of panel program in which both physicians and office assistants will find it in their best interest to participate.

Conclusion

I want to tell you again that regardless of the expected vicissitudes of an office of this character, it has been a privilege for me to serve as your President during the past 5 years. I wish to thank my co-workers on the Board of Trustees and various committees for their continued and dedicated support of Medical Service. I am especially grateful to the administrative staff who have rendered invaluable assistance to me during my presidency.

Finally, I want to extend my best wishes to my successor, whoever he may be. May he enjoy the excellent, dedicated support and coöperation I have received.

HENRY L. DARNER, M.D.
President

Health Dept. Notes

VD in D. C.

THE EDITORS of this journal and the leaders of the Medical Society have performed a true public service in making venereal disease the theme of this isssue of the MEDICAL ANNALS.

This will bring to the attention of all physicians practicing in the Washington area an excellent array of scientific articles on VD. It presents, at one time and in one place, a discussion of clinical and laboratory diagnosis of syphilis and gonorrhea; patient care, treatment and management; current research findings in VD; and a range of other topics.

There is also pertinent discussion of VD in Washington, the disease as it exists in our own community, with emphasis on the need for good epidemiology and follow-up of all case leads and contacts. This is the particular responsibility of the Health Department.

To meet this responsibility, however, we must have the active coöperation of the practicing physician. It is he who sees many, if not most, of the patients who have syphilis and gonorrhea. Our epidemiology must begin with that very first case and be followed to wherever it may go until we have traced its spread and hopefully intercepted its effects.

It is also our responsibility to aid the physician in his diagnosis of VD by offering medical laboratory services which are accurate and fast. This we do by using some of the most modern and definitive testing techniques which have been developed. These are discussed elsewhere in this journal.

It is our further responsibility to inform the public about the threat of venereal disease to themselves and to the entire community. This we do through group discussions, informational folders, educational films, stories in newspapers, and other means, all intended to stress the nature of VD and what can be done to control it. Much of this is aimed at teen-agers and younger adults, where we know there is a great amount of both syphilis and gonorrhea. Some of this material is developed for special audiences, such as the pioneer folder prepared in this Department on VD and the homosexual.

Our efforts in the public press and on radio and television are planned to enlist community support. We need as wide a base as possible on which to build our programs.

But we particularly require support by the medical profession in Washington. We need the physician's coöperation in our epidemiological investigations; his assurance to his VD patient that our concern does not violate privacy; his forwarding to our laboratories the necessary tests and specimens; his willingness to complete those few report forms asked of him; and, generally, his awareness that VD control must be a coördinated effort.

The present VD program in Washington began in earnest 3 years ago. The VD rate was high, both for syphilis and gonorrhea. It was especially high among younger persons here. This seemingly high rate may be due in part to our aggressive attempts to find and follow up all cases that could be discovered.

This rate has generally continued for the past 3 years. But now, for the first time in several years, the syphilis rate seems to be declining.

I cannot attribute this as yet to our efforts at control. I can say that there has been no relaxation in our program of finding and reporting. The decline therefore does not represent any easing by the Health Department. We find it, treat it, and report it as before.

I am not optimistic enough to try to read meaning into this decline. It is certainly too soon to ask interpretation by anyone. Let us therefore continue our controls, keep watch on the rate, and hope that perhaps we may be turning the corner on VD.

The American Medical Association has said that "venereal disease has become the Nation's most urgent communicable disease problem." The D.C. Department of Public Health shares that sense of urgency.

MURRAY GRANT, M.D., D.P.H.
D. C. Director of Public Health

Dr. Kurtz to Head Cancer Society

DR. C. ROGER KURTZ, well-known Washington physician, was elected President of the D. C. Division of the American Cancer Society at the meeting of its Board of Trustees, June 9, to take office September 1. At the preceding Annual Meeting in the D. C. Medical Society Building, he was presented the St. George Medal and Citation for outstanding contributions to cancer control.

Dr. Kurtz has served the past year as Vice President of the D. C. Cancer Society and as a member of the Executive Committee of the Board of Trustees. He has been an active volunteer with the Cancer Society for 12 years. Especially interested in direct services to cancer patients, he has served as Vice Chairman for several years of the Society's Service Committee. He is a graduate of Jefferson Medical College, Class of 1939. During World War II he was commissioned Captain in the Army Medical Corps and served in the South Pacific Area. He is a member of the American Medical Association, the American Academy of General Practice, the D. C. Medical Society, and the Medical Arts Society of Greater Washington.

Dr. Peter D. Comanduras and Dr. Ernest A. Gould were elected Vice Presidents of the Society. Among those newly elected to the Board of Trustees were Drs. William J. Jaffurs, Philip H. Philbin and K. Albert Harden. Among those reëlected to the Board for a 3-year term were

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When readings indicate hypertension, start with Naturetin, stay with Naturetin.

Contraindications: Severe renal impairment; previous hypersensitivity.

Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available—Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

References: 1. Telfeyan, S. A.: Clin. Med. *70*:1668, 1963. 2. Shepard, H. L.: J. Am. Geriatrics Soc. *11*:363, 1963. 3. Cummings, D. E.; Goodman, R. M., and Steigmann, F.: J. Am. Geriatrics Soc. *12*:161, 1964. 4. Castleman, B., ed.: New England J. Med. *268*:1462, 1963.

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Dr. Kurtz, newly elected President of D. C. Cancer Society

Drs. Gould, A. F. Castro, J. Keith Cromer, Robert S. Jason, and George W. Ware.

Seven physicians were awarded Certificates of Appreciation for conducting 25 or more cancer educational programs for the general public. They were: Drs. I. Phillips Frohman, R. Stephen Hulburt, LaSalle D. Lefall, Samuel Q. Mitchell, John F. Potter, and Cyril Schulman, of Washington, and Joseph C. Smith, of Silver Spring, Md.

Mr. William P. McClure, Crusade Chairman, reported that the 1966 goal of $600,000 had already been exceeded. He was awarded a Certificate for Meritorious Service for heading the Crusade for the past 11 years.

Mr. Leonard J. Emmerglick, retiring President, described 2 immediate objectives of the Society, a cancer patient counseling service in each hospital and the promotion of memorials for lives that are saved from death by cancer as well as those who succumb to the disease. In this way, he said, people will learn to associate cancer with life and not only with death. Mrs. Verna S. Cook, R.N., recipient of an ACS fellowship to Memorial Hospital for Cancer and Allied Diseases, stated the nurse's view of cancer, which was, briefly, "Every cancer patient can be helped." Many can be saved, she said, and about one third are cured.

Patients Needed at Clinical Center

Hyper- or Hypoparathyroidism. The coöperation of physicians is requested in a study of patients with either hyper- or hypoparathyroidism in conjunction with developing a practicable immunoassay for parathyroid hormone being conducted by the National Institute of Arthritis and Metabolic Diseases at the Clinical Center, National Institutes of Health, Bethesda, Md.

Of interest for this study are patients with kidney stones and/or bone demineralization in association with high serum calcium and/or low serum phosphate. Patients with hypoparathyroidism (congenital or following extensive thyroid surgery) having low blood calcium and high serum phosphorus are also needed.

Physicians interested in having their patients considered for admission to the Clinical Center for this study may write or telephone Dr. Gerald D. Aurbach, Clinical Center, Room 9-D-14, National Institutes of Health, Bethesda, Md. 20014; telephone: 656-4000, Ext. 65051.

Cystinuria. The National Institute of Arthritis and Metabolic Diseases also requests referral of patients in order to study the basic nature of cystinuria and newer forms of treatment of patients with this disorder. Patients with severe calculus disease will be considered for participation in the study.

Physicians interested in having their patients considered for this study may write or telephone Dr. Stanton Segal or Dr. John Crawhall, Clinical Center, Room 8-N-256, National Institutes of Health, Bethesda, Md. 20014; telephone: 656-4000, Ext. 63010.

Hodgkin's Disease and Lymphosarcoma. The coöperation of physicians is requested in a study of Hodgkin's disease and lymphosarcoma being conducted by the National Cancer Institute at the Clinical Center.

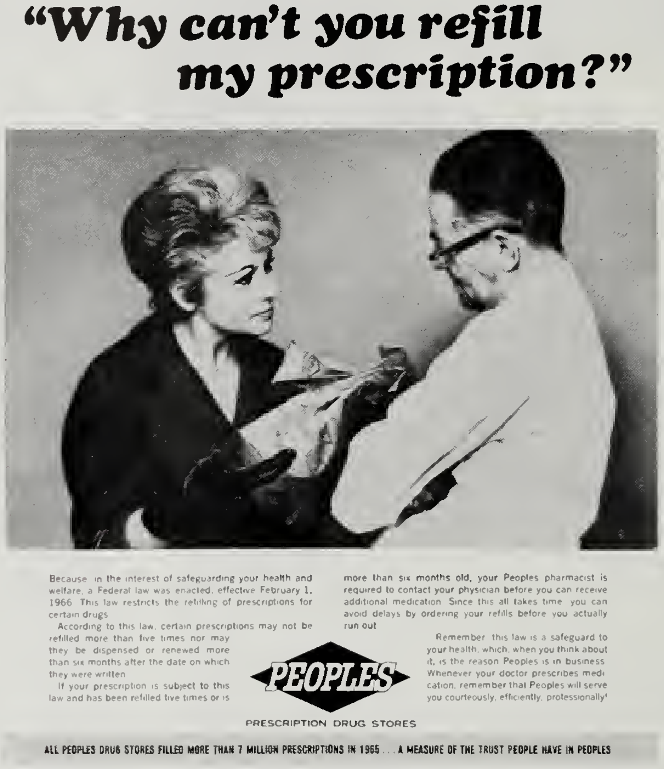
Particularly desired are patients who have had no previous treatment or minimal prior treatment. All clinical stages of biopsy-proven disease are acceptable. The major purpose of the study is to determine the curative potential of intensive radiotherapy in localized cases and to evaluate combination chemotherapy and X-irradiation in patients with generalized involvement.

Physicians interested in having their patients considered for the study may telephone or write to Dr. Paul P. Carbone, Clinical Center, National Institutes of Health, Building 10, Room 12-N-228, Bethesda, Md. 20014; telephone: 656-4000, Ext. 64251.

Chronic Lymphocytic Leukemia. A study of chronic lymphocytic leukemia, including therapy in patients with this disorder, is being conducted by the Medicine and Radiation Branches of the National Cancer Institute at the Clinical Center. Referrals of selected patients, particularly those with high circulating lymphocyte counts, are needed.

Physicians interested in having their patients considered for the study may write or telephone Dr. Carbone.

Should a determined lady always have the last word?



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NEWS & PERSONALS

Summary of Executive Board Actions

Proceedings of May 23 Meeting

Dinner for the Executive Board members was served at 6:30 p.m. in the Exhibit Hall of the Medical Society of the District of Columbia, May 23. Dr. J. Spencer Dryden, Chairman, presided over the meeting which followed in the Board Room. Present were Drs. C. Willard Camalier, Jr., Robert J. Coffey, Karl C. Corley, Henry D. Ecker, Claudine M. Gay, Raymond T. Holden, Edward W. Nicklas, Lawrence A. Rapee, and Mr. George W. Cooley, Secretary. Also present were Drs. Ralph D. Whitley, Brooks G. Brown, O. Hugh Fulcher, and Josephine E. Renshaw, the Society's representatives on the Board of Trustees of Group Hospitalization, Inc. The meeting opened at 7:30 p.m.

The minutes of the meeting of April 25, which had been mailed previously, were approved.

Committee Meetings: The following committee meetings were reported by the Secretary as having been held since the Board last met:

April 23 Committee on Environmental Health
29 Committee on Medical Aspects of Sports and Physical Fitness
May 3 Committee on Relative Value Study
4 Committee on Child Welfare
4 Advisory Group on P.L. 89-239
6 Fee Review Committee
11 Committee on Constitution and By-laws
16 Insurance Committee
17 Grievance Committee
18 Ad Hoc Committee on Health Foundation of D. C.

Society's Representatives on Board of Trustees of GHI: The Chairman welcomed Drs. Whitley, Brown, Fulcher, and Renshaw to the meeting and asked Dr. Fulcher to review his first letter to the Executive Board.

Dr. Fulcher explained briefly that the purpose of his letter was to request guidance for himself and the other Society representatives so that they might better serve as members of the Board of Trustees of GHI. He pointed out that this was the first time in all the years that he had represented the Society on the GHI Board that he had met with the Society's Executive Board to discuss problems encountered by GHI. He referred particularly to the problem having to do with local hospitals resigning as participating hospitals.

Following this there were many questions raised by the Executive Board members and considerable discussion in reference to them. It was agreed that a future meeting of the Board should be devoted to a continuing discussion of the questions raised and the problems brought out at this meeting.

It was voted that a letter be written to the President of GHI and that letters be sent to the Chairman of each Hospital Board in the District expressing the concern of the Medical Society over the growing estrangement between GHI and some hospitals and seeking to determine whether or not every possible effort is being made to again bring GHI and these local hospitals into accord.

Building Fund: The Secretary reported that a 20-year loan for $500,000 at 5 per cent had been obtained, to be paid quarterly in the amount of $6,250. He pointed out that after paying all prior loans and the interest, the balance in the building fund was $172,914.88. He also pointed out that payments due to the builder and architect on completion of the building as well as funds to be returned to the General Fund from advances would reduce the net balance to approximately $21,000.

Committee on Society Insurance Programs:

A. The Secretary reported on a new Group Life Insurance Program to be offered to the members in June, underwritten by United Benefit Life Insurance Company. It was agreed that the letters to accompany the brochure should be signed by the Committee Chairman and countersigned by the Chairman of the Executive Board.

B. The Secretary reported on the fact that the premiums for the Society's Health and Accident Insurance Program would remain stable during the coming year.

C. The Secretary reported that the Committee had reviewed with representatives of Blue Cross-Blue Shield the possibilities of altering the program for those over 65. The 2 choices are: (1) to leave the program as is, and if there is any benefit derived from the use of Medicare by doctors over 65 it should show up in a premium reduction; (2) to offer a special program for those over 65 under which GHI and Medical Service would pick up where Medicare left off, but would leave the physician over 65 the necessity of signing up for Part B or having to pay that portion himself. Since there was no way of knowing how many physicians have signed up for Part B, the Committee chose to leave the program as is for the coming year. This means that physicians over 65 now in the program could remain and pay present rates or could individually join the BC-BS "over 65" program.

D. The Secretary reported that the Committee was considering a retirement program proposal for Society members which would be reported later to the Executive Board.

Status under Project P.L. 89-239: Since Dr. Desmond S. O'Doherty could not be present, Dr. Coffey reported briefly on the progress being made in completing the Application for a Planning Grant. He pointed out that Dr. O'Doherty hoped to have it completed by June 15.

Doctor's House Call: The Secretary reported on a request from Kal, Ehrlich & Merrick to have the Society approve a letter to its members describing the program, "Doctor's House Call," together with a small table poster to be distributed to doctors for use in their offices. The question was raised as to whether or not this had been acted upon by the Committee on Public Information and Education. Since the answer was no, it was voted to refer this matter to the Committee on Public Information and Education.

Committee on Relative Value Study: The Secretary distributed a memorandum from Dr. Frank Bacon, Chairman of this Committee, briefly outlining the progress being made on the Relative Value Scale. It was voted that the Committee be authorized to expend such funds as are necessary to complete its task in revising the Relative Value Scale.

Miscellaneous Business

A. Dr. Holden reported that the Red Cross had created a Medical Advisory Committee and had asked him to serve as Chairman. He reported briefly on the function of the Committee and said that its makeup would include 4 subgroups: Disaster, Blood, Nursing, and Injuries. Dr. Holden was authorized to prepare a list of Committee members to be submitted to the Red Cross and to assure the Red Cross of the Society's desire to coöperate in any tasks undertaken by this Medical Advisory Committee.

B. The Secretary reported that a reply had been received from Judge Hart assuring Dr. Dryden that the Society's recommendation that Dr. Preston A. McLendon be reappointed to the Board of Education would receive the attention of the Judges of the Court.

C. It was voted to co-sponsor the following Seminars with the Health Department as recommended by the Committee on Communicable Diseases:

Salmonellosis—June 23, 1966
Immunizations—September 22, 1966
Viral Hepatitis—October 20, 1966
Tuberculosis—February 16, 1967

The Health Department will take care of expenses, including honorariums. The Seminars will be held at the Society's headquarters.

D. Community Health Week. The Secretary reported the general outline of the Committee's proposals for Community Health Week, October 16–22, 1966. The Committee will report further following a meeting with representatives of various local health groups.

He reported also that the only time open for the Society's Annual Luncheon during the Southern Medical Association was on the last day, a Thursday, and that Dr. Warren D. Brill had asked that the Executive Board permit this luncheon to be held as a part of Community Health Week and in coöperation with some of the local health agencies.

It was agreed that the Annual Society Luncheon could be held during Community Health Neek if the Committee so desires and if proper arrangements can be made.

E. The Secretary reported that a hearing is to be held on the Health Department's proposal for Hospital Regulations and Licensure and that he had received the statement of the Hospital Council on May 20. He distributed a suggested statement on behalf of the Medical Society in support of the recommendations being made by the Hospital Council. It was voted that since the Chairman of the Executive Board could not be in attendance at 2:00 p.m., Wednesday, May 25, President Coffey present this statement and represent the Society.

F. Medical Annals Advertising. The Secretary reported briefly on the need for an increase in certain charges for advertising. It was voted to approve the increases suggested by the Secretary.

There being no further business, the meeting was adjourned.

General News

Women physicians are being urged to enlist for immediate active duty in the Armed Forces in order to meet the medical requirements of the Army in connection with current Southeast Asian hostilities. The Army guarantees initial assignments in Continental United States unless overseas areas are desired. However, women physicians will not be involuntarily assigned to an overseas area during the initial tour of active duty.

As commissioned officers, women physicians enjoy all the benefits of laws and regulations pertaining to pay, promotion, and retirement. Interested women physicians should apply to The Surgeon General, Attn: MEDPT-MP, Department of the Army, Washington, D. C. 20315. Grades for which women physicians are eligible may range from captain to lieutenant colonel, depending on age, experience, and professional qualifications. Applications will be accepted for periods of active duty of 2 years or longer.

Applications from research investigators for support of studies to be conducted during the fiscal year beginning July 1, 1967 are now being accepted by the **American Heart Association.**

Established Investigatorships, with a stipend of $11,000 and increments of $1,000 yearly, are awarded for 5 years to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. An additional $1,000 is given as a grant to the investigator's institution.

Advanced Research Fellowships are awarded for 1- or 2-year periods to postdoctoral applicants who have at least 2 years of research training and experience at time of application but who are not clearly qualified to conduct their own independent research. Stipends begin at $6,500, plus dependency allowances and yearly increments. An additional $500 is granted to the Fellow's institution.

September 15, 1966 is the deadline for submitting applications for Established Investigatorships and Advanced Research Fellowships. Application forms may be obtained from the Director of Research, American Heart Association, 44 East 23rd Street, New York, N. Y. 10010.

Applications for Grants-in-Aid should be submitted by November 1, 1966. Grants-in-Aid are made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

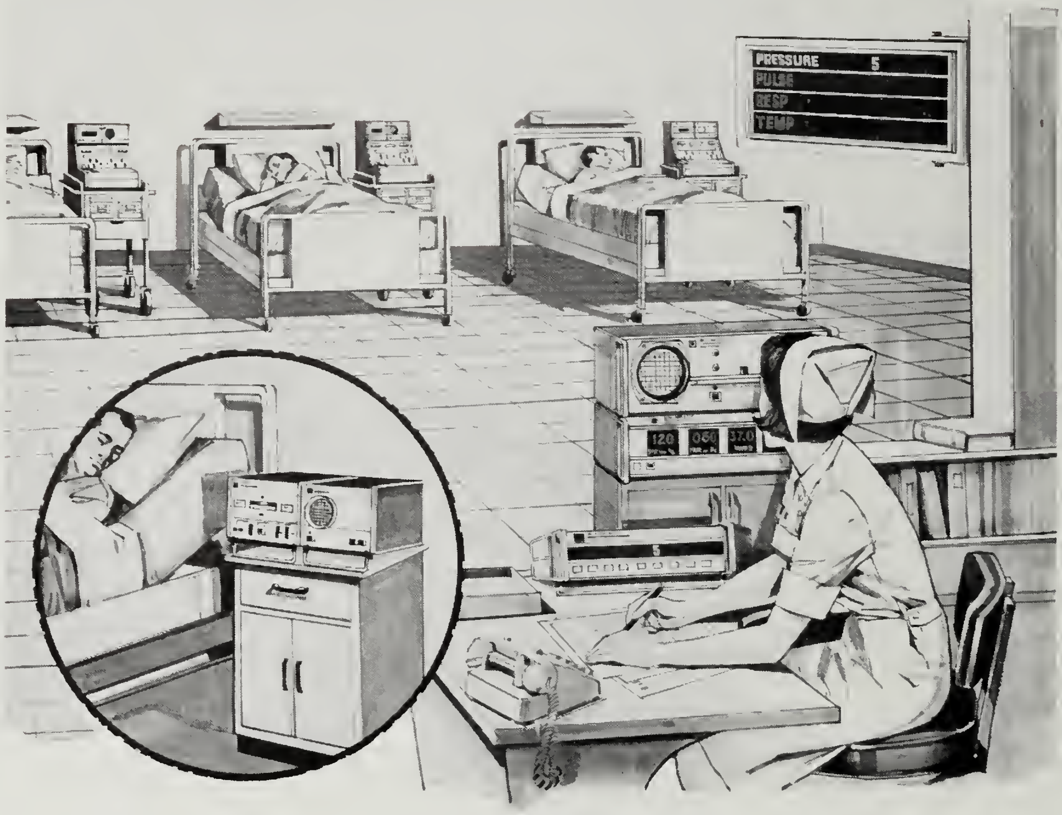
Officials of Group Hospitalization, Inc. list the following hospitals in the Washington Metropolitan Area as having chosen Blue Cross to serve as their Medicare fiscal intermediary: Arlington, Casualty, Children's, Doctors, Fairfax, Freedmen's, George Washington University, Georgetown University, Leland Memorial, Morris Cafritz Memorial, National Orthopaedic, Northern Virginia Doctors, Prince George's General, Providence, and Sibley; also, the hospital facilities of the D. C. Department of Public Health, namely, D. C. General Hospital, Glenn Dale Hospital, and Area C, Community Mental Health Center.

In the area of home health services, the Visiting Nurse Association of Washington and Home Care Services Division of D. C. Public Health Department have selected Blue Cross as Medicare intermediary.

Georgetown University School of Medicine has announced the appointment of 2 new department heads, effective July 1, 1966.

Dr. John R. Paul, Jr., Professor of Pediatrics, will also serve as Director of Georgetown's Mental Retardation Program. A native of Charleston, S. C., Dr. Paul received his medical degree from the Medical College of South Carolina in 1942. He entered the private practice of pediatrics in Charleston in 1948 and at the same time joined the faculty of his alma mater as Clinical Instructor in Pediatrics. In 1958 he was appointed Professor and Chairman of the Department of Pediatrics, a position he has held up to the present time.

Dr. Paul D. Bruns succeeds Dr. Andrew A. Marchetti as Professor of Obstetrics and Gynecology and Chairman of the Department. Dr. Marchetti will remain at Georgetown as Professor of Obstetrics and Gynecology; he is currently



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President of the American Gynecological Society.

Dr. Bruns graduated from the University of Iowa School of Medicine in 1941. He served in the Medical Corps of the United States Army from 1942 to 1946, achieving the rank of Major. After residency training in obstetrics at Johns Hopkins University Hospital from 1945 to 1949, he joined the faculty of the University of Colorado School of Medicine as Assistant Professor of Obstetrics and Gynecology, attaining the rank of Professor in 1957.

The George Washington University Medical Alumni Association, at its annual banquet, May 28, at the Statler Hilton Hotel, installed into office Dr. George Speck as President. He succeeds Dr. Richard E. Palmer. Other new officers of the Association are:

Dr. Jerome Epstein, *President-elect;* Dr. William Brainin, *First Vice President;* Dr. James A. Dusbabek, *Second Vice President;* Dr. Jack Kleh, *Secretary;* and Dr. Charles E. Smith, *Treasurer.*

At the annual banquet an Alumnus Award was presented to Dr. James L. Goddard, Food and Drug Commissioner, who received his medical degree from George Washington in 1949; Dr. Paul Calabrisi, Professor of Anatomy, was cited for meritorious service to the Association, the University and the community.

New officers of the **Jacobi Medical Society** are:

Dr. Morris E. Krucoff, *President;* Dr. Arthur J. Wilets, *Vice President;* Dr. Morton H. Rose, *Secretary;* and Dr. Stanley M. Silverberg, *Treasurer.*

Dr. Edward Adelson, the new President-elect, will take office in 1967.

At a recent meeting of the **Washington-Baltimore Society of Physical Medicine and Rehabilitation,** the following officers were elected for 1966–67:

Dr. Frederick J. Balsam, Baltimore, *President;* Dr. David A. Zohn, Washington, *Vice President;* and Dr. B. Stanley Cohen, Baltimore, *Secretary-Treasurer.*

The National Capital Occupational Medical Association elected new officers at its business meeting, May 25. Captain John H. Schulte, MC, USN, President, is Director of the Submarine Division of the Navy Department. Dr. William T. Doran, Vice President, is with the Division of Operational Safety of the U. S. Atomic Energy Commission. The Secretary-Treasurer is Dr. Lawrence A. Pyle, Jr., Medical Director of the Chesapeake and Potomac Telephone Company.

Serving on the Board of Directors are Dr. Gordon S. Siegel, Bureau of Medical Services, PHS; Dr. Malcolm D. Harrison, of the Potomac Electric Power Company; and Colonel Frank Bowling, USAF, MC, of the Office of Surgeon General, USAF. Dr. Marcel J. Foret, of the Western Electric Company, who was elected delegate to the Industrial Medical Association, is an ex officio member of the Board.

The Visiting Nurse Association of Metropolitan Washington dedicated its new Edward W. Fay wing, June 6. Built at a cost of $115,000, the 3-story addition to 1842 Mintwood Place is named for a long-time Board member and former Treasurer of the Association. Mr. Fay, who died 3 years ago, had been Treasurer of VNA since 1948. In his will he left one half of his residual estate to the Nurses. He and the rest of the Board had shared the goal for many years of bringing the VNA endowment up to $1 million, and his bequest accomplished that objective.

The new wing was dedicated by the former Bishop of Washington, Angus Dun. Mrs. Fay was among those who attended the simple dedication ceremonies.

Dr. Malcolm E. Phelps, of El Reno, Okla., a member of the House of Delegates of the American Medical Association and Past President of the American Academy of Pediatrics, has assumed the new post of **field director of Project Vietnam.** The State Department's Agency for International Development enlisted the support of the AMA in order to encourage more physicians to volunteer for service in South Vietnam.

Dr. Phelps left for Vietnam on July 1, to be gone about 6 months. From his headquarters in Saigon he will maintain liaison between volunteers and USAID, visit the 16 provincial hospitals where volunteers are stationed, and provide orientation for newly arrived volunteers.

Dr. Roy F. Perkins, who has been in the practice of internal medicine with the Alhambra (California) Medical Clinic since 1951, has been named **Director of the newly established Department of Health Care Services** at the American Medical Association, effective July 1.

The Department of Health Care Services is one of 6 departments of the Division of Socio-Economic Activities. This department will be concerned with community health services, voluntary health agencies, aging, maternal and child care, group practice, insurance and prepayment, patterns for the organization and delivery of medical care, manpower, and the business side of medical practice.

Dr. William J. Brownlee, Chief Admitting Officer at D. C. General Hospital since 1964, has been **named Deputy Coroner** by District Coroner Richard L. Whelton. Dr. Brownlee succeeds Dr. Jorge B. Morales, who resigned in 1963. The new Deptuy is a graduate of Howard University College of Medicine.

Mr. William W. Gibson, Sr., President of the Gibson Company, died June 4, 1966. Mr. Gibson had headed the company at 922 19th Street, N.W. since about 1935. He joined the surgical supply firm, founded in 1907 by his father, William Gibson, in 1919. He leaves 2 sons, William W., Jr., of Alexandria, Va., and Harry S. Gibson, of the home address, 4417 Upland Drive, Alexandria.

The Gibson Company has been represented in the advertising pages of the Medical Annals since its first issue in 1932, and previously, in the Society's *Bulletin*.

Personals

Dr. William P. Herbst has accepted several new offices to which he has recently been elected or appointed. The American Association of Genitourinary Surgeons, at its meeting, May 25–27, in Oakbrook, Ill. elected him Vice President. He was appointed Chairman of the Research Committee of the American Urological Association at its meeting, May 30–June 2, at the Palmer House in Chicago. He will also represent the American Board of Urology for a 3-year period on the Residency Review Committee in Urology.

Dr. Gordon S. Siegel, an Associate member of the D. C. Medical Society, has been appointed Chief of a new Division of Federal Employee Occupational Health and Safety, effective June 1. The new Division combines the work of the Federal Employee Health Program, which has been a part of the PHS Division of Hospitals, and the Safety and Fire Prevention Section, which has been a part of the Office of the Surgeon General. The Division is in the PHS Bureau of Medical Services in Silver Spring, Md.

Dr. Charles A. Hufnagel, Professor of Surgery at Georgetown University School of Medicine, received an honorary degree from the University at its commencement exercises, June 6. Dr. Hufnagel was recognized for his pioneer contributions in the field of heart surgery.

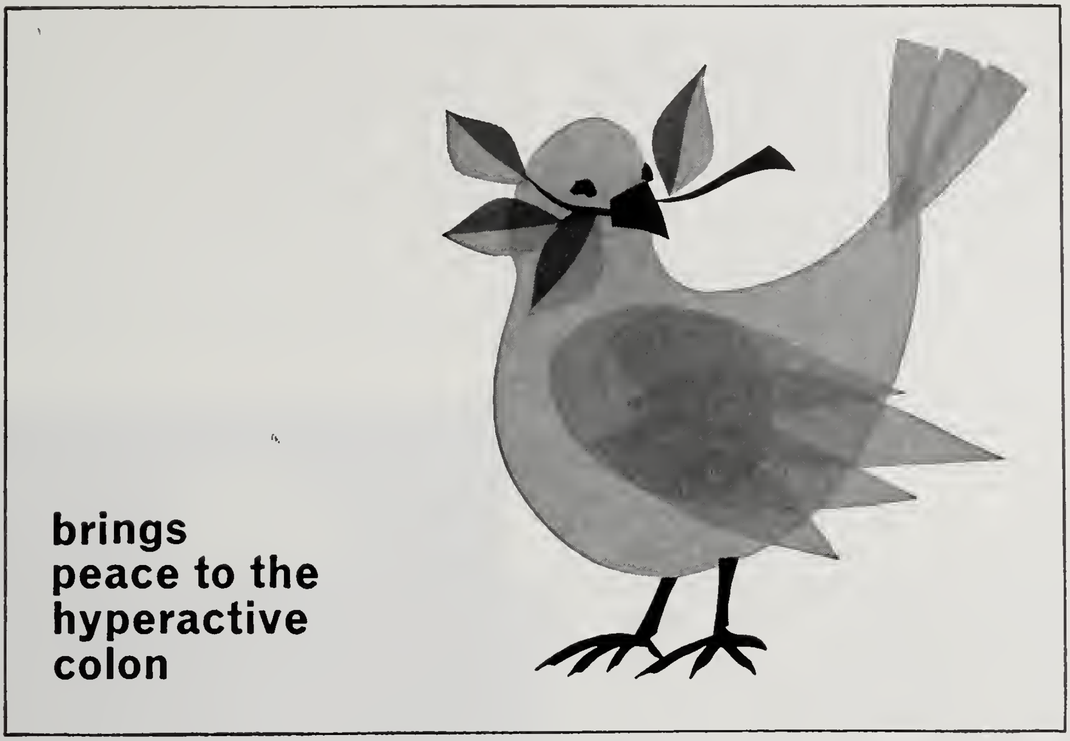
Dr. Clifton R. Brooks has been appointed to the Resolutions Committee of the Aerospace Medical Association.

Among those inducted into Fellowship in the American College of Physicians during the 47th Annual Session of the College in New York City, April 18–22, were: **Drs. Habeeb Bacchus, Thomas M. Brown, James J. Foster, Clifton K. Himmelsbach, George A. Kelser, Jr., John A. Kenney, Jr., Rashid A. Massumi, and Frank J. Talbot**, all Active members of the D. C. Medical Society except Dr. Himmelsbach, who is an Associate member.

The name of **Dr. Eugene J. McDonald** was omitted from the list of donors to the furnishings of the new Medical Society building which appeared in the May issue of the Medical Annals. Dr. McDonald made a substantial contribution and the error is deeply regretted.

Six members of the D. C. Medical Society were among the proud parents who witnessed the commencement exercises at George Washington University School of Medicine, June 5. Included in the Class of 1966, which consisted of 85 men and 2 women, were Drs. William P. Chalfant, Luther W. Gray, Jr., Thomas S. Neviaser, David R. Notes, Ronald E. Smith, and Howard S. Yager. In addition to the sons, congratulations were extended to the fathers, namely, Drs. W. Paxton Chalfant, Luther W. Gray, Julius F. Neviaser, Bernard Notes, A. Leonard Smith, and Irwin I. Yager. Drs. Neviaser, Notes, and Smith are also alumni of George Washington University.

At the Medical School Closing Assembly, June 3, **Dr. Leon Yochelson**, Chairman of the Department of Psychiatry, was chosen by the Class of 1966 to deliver the principal address.



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1. Riese, J. A.: Amer. J. Gastroent. 28:541 (Nov.) 1957

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A DIET COUNSELING SERVICE to aid physicians and to benefit those patients suffering from all forms of cardiovascular disease, including stroke, has been added to the free programs of the Washington Heart Association, according to Dr. John F. Finnegan, President.

The new service is designed to give nutritional counseling to cardiovascular patients as part of their medical treatment on physician referral. A trained nutritionist is available for consultation in the offices of the Washington Heart Association or, on request, in the doctor's office. Where a patient is confined to bed in the home, arrangements for home visits may be made by the physician.

The Washington Heart Association will supply the doctor with special nutrition referral pads on request. These may be used to pinpoint the type of diet prescribed for the patient and will serve as a guide to the nutritionist.

Information on how to adapt specific types of diets, such as modified fat diets, 500, 1,000 mg. or more sodium diets, etc., will be prepared by the nutritionist for the patient's use in accordance with the doctor's prescription and explained to the patient. A new leaflet will be available giving the sodium content of various foods and advising where they may be purchased in the Washington area.

Further information on the new diet counseling service may be obtained at the offices of the Washington Heart Association, 2007 Eye Street, N.W., telephone 296-4697.

Retirement of Dr. Paul F. Dickens*

MRS. SMITH: "Madam President, one of America's most distinguished physicians is retiring after 60 years of eminently successful practice of medicine. He is Dr. Paul F. Dickens, who has distinguished himself not only in the practice of medicine but with an outstanding career in the U.S. Navy. He has been the confidant and close friend of Presidents, Senators, Representatives, diplomats, and other national and international leaders. In these relationships he has had great influence with respect to our national policies and with respect to individual careers.

"After a notable career in the Medical Corps of the U.S. Navy, Dr. Dickens retired from the Navy and entered the private practice of medicine in Washington in 1938 to become one of the city's leading internists. He has been associated with Dr. Walter A. Bloedorn, both while Dr. Bloedorn was Dean of the George Washington University and Medical Director of the George Washington University Hospital, and thereafter.

"Previous to his retirement from the Medical Corps of the U.S. Navy, Dr. Dickens was the Head of the Department of Medicine and Cardiology at the Navy Medical School, where he became nationally famous for his diagnostic skill and his teaching talents with its personnel and the training of his fellow officers.

PAUL F. DICKENS, M.D.

"During a previous 3-year term of Navy duty in Haiti, he was the recipient of a letter of commendation from the Surgeon General of the Navy for his work in bacillary dysentery, and later for an article on choriomeningitis, its cause, diagnosis, and treatment. Similar commendation followed his article disclosing that aseptic meningitis should be classified as caused by a virus.

"In 1938, in conjunction with Dr. Charles Armstrong of the Public Health Service, the *Journal of Modern Medicine* nominated Dr. Dickens and Dr. Armstrong for consideration as the Doctors of the Year. Subsequently, Dr. Dickens was the recipient of a grant from the George Washington University Medical School for a Study of high blood pressure.

"In World War II, Dr. Dickens served as Chairman of the Manpower Commission for Physicians in addition to carrying on the demands of his private practice. For this service to his country, President Truman presented him with a certificate of thanks and a Medal of Merit.

"A former Professor of Medicine at the George Washington University Medical School, Dr. Dickens is

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*EDITOR'S NOTE: This is a warm, affectionate appraisal of the professional career of one of the District Medical Society's eminent members, Dr. Dickens, by the distinguished Senator from Maine, Margaret Chase Smith. It appeared in the *Congressional Record* of January 24, 1966, and is reprinted in part herewith.

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Professor Emeritus of Medicine at the George Washington University. Previous to his association with the George Washington University Medical School, Dr. Dickens served as Associate Professor of Medicine at the Georgetown University School of Medicine.

* * * * *

"Yes, Paul F. Dickens has been an eminent leader in many fields. He has been an unexcelled physician of amazing knowledge and talents, who has kept fully abreast of medical progress and scientific changes. But more than that, he has possessed a special kind of healing capacity that rarely anyone is endowed with. It is that special way of human kindness which does as much if not more than all medical knowledge in the treatment and recovery of patients.

"He has an abundance of what tragically so few possess. It is an abundance of empathy. I know, for he was the personal physician of my late husband. I know, because he has been my personal physician. I know, because it was Dr. Paul F. Dickens who urged and convinced me that I should run for election to succeed my husband after his death. I know, because it was Dr. Paul F. Dickens who literally launched me on my public service career."

Obituaries

Aris Carpousis, B.S., D.D.S., M.D.

(1916–1966)

Dr. Aris Carpousis, flight surgeon, dentist and sportsman, died, April 14, 1966, while playing tennis at the Army-Navy Club in Arlington, Va.

Dr. Carpousis was born in Samos, Greece, November 9, 1916. His father, Agamemnon Carpousis, a Washington and Greek philanthropist, died a year ago. The family came to the United States when Dr. Carpousis was 4 years old and settled in Reading, Pa., where he graduated from high school and Albright College with honors. He received a scholarship to study dentistry at Temple University, where he obtained his degree in dental surgery in 1942. Four years later, 1946, he received his medical degree from Hahnemann Medical College in Philadelphia.

He interned at the U. S. Marine Hospital at Staten Island, N. Y., the following year. From 1947 to 1950 he was on active duty, with the commission of Captain, with the U. S. Air Force, serving as flight surgeon and aviation physiologist. Since 1950 he had engaged in the private practice of medicine in the District of Columbia.

Dr. Carpousis was wing flight surgeon for the Washington Civil Air Patrol and was certified as a flight examiner. He was among the founders of the Civil Aviation Medicine Association and the Aerospace Medical Association.

Dr. Carpousis was certified by the American Board of Preventive Medicine. He was a member of the American Medical Association, an Active member of the Medical Society of the District of Columbia since 1950, a member of the American Academy of General Practice, the American College of Preventive Medicine, and the District Dental Society. He belonged to the Army-Navy Club, the Order of Ahepa, the Odd Fellows, and he was a 32nd degree Mason.

Dr. Carpousis had many interests. He distinguished himself in sports while in high school and college. A talented musician, he was director of a small Doctors' Orchestra which played at various hospital charity events.

He leaves his wife, Mrs. Mary Heon Carpousis; 3 sons, Aris, Jr., Dean and Gregory; and 3 daughters, Fern, Pamela and Catherine, all of the home address, 3500 Garfield Street, N.W.

Wendell Maurice Lucas, B.S., M.S., M.D.

(1920–1966)

Dr. Wendell M. Lucas, a brilliant and popular professor at Howard University College of Medicine, died, May 2, 1966, at the Washington Hospital Center following a long illness.

Dr. Lucas was born to Townsend M. and Cynthia Johns Lucas in Washington, D. C., February 21, 1920. He graduated with honors from Howard University in 1940 and received his Master's degree in chemistry, also from Howard, in 1942.

With World War II in progress he enlisted for duty with the U. S. Air Force, serving from 1942 to 1946 with the commission of Captain. As Commander of the 99th Fighter Squadron in Italy he flew 40 combat missions and was awarded the Air Medal with 3 Oak Leaf Clusters for meritorious service.

After the War he returned to Howard to begin the study of medicine and graduated in 1950 at the head of his class. He interned for a year at the U. S. PHS Hospital in Staten Island, N. Y. and followed this with 3 years of resident training in surgery and urology at Freedmen's Hospital. He studied as a Fellow in Urology at the Memorial Center for Cancer and Allied Diseases in New York and at Johns Hopkins University School of Medicine in Baltimore. He was certified by the American Board of Urology.

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Side effects: Occasional lightheadedness or transient itching which may disappear with continued use. There are no known contraindications; however, caution is advised when there is a concomitant administration of a coronary vasodilator.

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He had served on the faculty of Howard University since 1954, and at the time of his death he was Chief of the Division of Urology, Department of Surgery, and Chief of Urology at Freedmen's Hospital. In 1958 the Student Council of Howard University selected him as the outstanding teacher of the year.

He was a Fellow of the American College of Surgeons, a member of the American Medical Association, the National Medical Association, an Active member of the Medical Society of the District of Columbia since 1956, and a member of the Medico-Chirurgical Society of D. C. He belonged to a number of honorary scientific societies, including Kappa Mu, Sigma Xi, and Phi Beta Kappa.

Surviving him are his wife, Mrs. Jane Marshall Lucas, of 1605 Buchanan Street, N.W.; 4 children, Marshall, Wendell M., Jr., Cynthia, and Shelly Jane. His mother, Mrs. Cynthia M. Early, also survives him, together with 2 brothers, Elliott W. Lucas, of Washington, and Townsend M. Lucas, of Englewood, N. J.; also a sister, Mrs. Constance L. Drew, of Washington.

Laboratory Diagnosis of Venereal Disease—Schepers

(Continued from page 366)

modification of the FA technique exploits fluorescein-isothiocyanate, conjugated antigonococcus globulins, rabbit normal globulin, or anti-staphylococcus aureus 193 globulin. With this variation the gonococcus shows green fluorescence against an orange background and therefore is quite quickly perceived and identified. This type of specific or differential fluorescence will hopefully lead to automation or semi-automation by exploiting appropriate photometric attachments to the microscope. Mass production of accurate results should then be possible.

In summary, we may then present table 14 which outlines the criteria which must be met to establish a laboratory diagnosis of gonorrhea.

Venereal Disease Research—Lucas

(Continued from page 378)

controls were reactive. Unfortunately, the results obtained by Reising for the important female category are not statistically different from Magnusson's. This area of study remains a challenging one.

In conclusion, let me but point out that many of the finest minds in medical science were attracted to the study of venereal disease throughout the pre-antibiotic era. Names like John Hunter, Ricord, Fournier, Schaudinn, Hoffman, Wassermann, Ehrlich, Noguchi, Neisser, Osler, Zinsser, and Stokes are replete in the annals of venereology. The current resurgence of the venereal diseases will, hopefully, again attract a new generation of medical scientists to confront man's age-old adversary.

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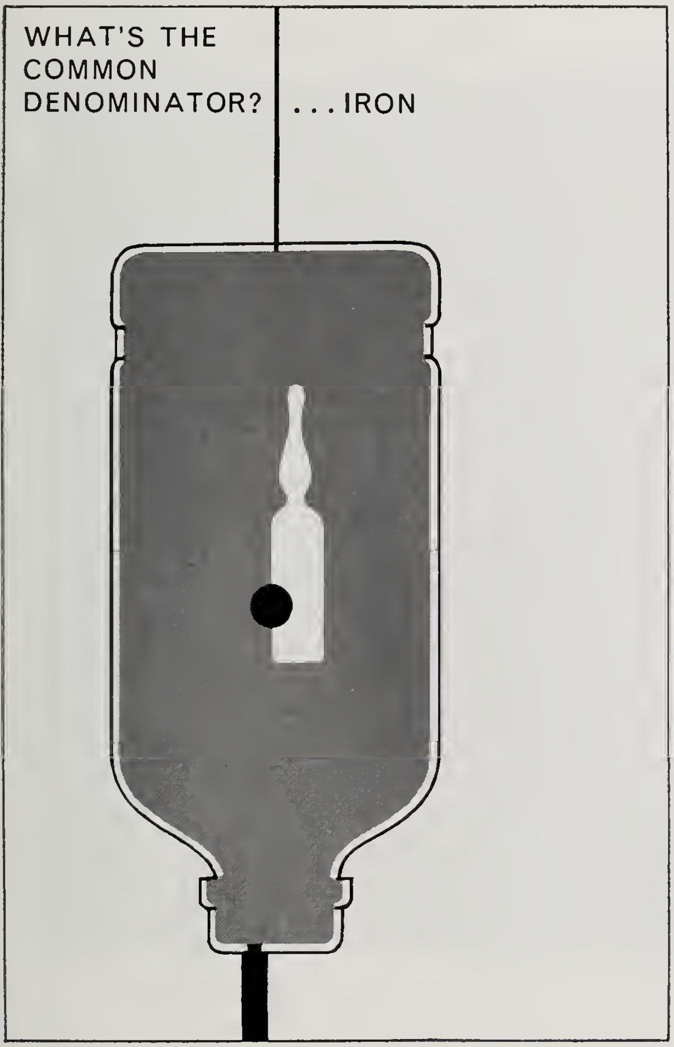

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COMPOSITION: Imferon (iron dextran injection) is a well-tolerated solution of iron dextran complex providing an equivalent of 50 mg. in each cc. The solution contains 0.9% sodium chloride and has a pH of 5.2-6.0. The 10 cc. vial contains 0.5% phenol as a preservative.
ADMINISTRATION AND DOSAGE: Dosage, based upon body weight and Gm. Hb/100 cc. of blood, ranges from 0.5 cc. in infants to 5.0 cc. in adults, daily, every other day, or weekly. Initial test doses are advisable. The total iron requirement for the individual patient is readily obtainable from the dosage chart in the package insert. Deep intramuscular injection in the upper outer quadrant of the buttock, using a Z-track technique, (with displacement of the skin laterally prior to injection), insures absorption and will help avoid staining of the skin. A 2-inch needle is recommended for the adult of average size.
SIDE EFFECTS: Local and systemic side effects are few. Staining of the skin may occur. Excessive dosage, beyond the calculated need, may cause hemosiderosis. Although allergic or anaphylatoid reactions are not common, occasional severe reactions have been observed, including three fatal reactions which may have been due to Imferon (iron dextran injection). Urticaria, arthralgia, lymphadenopathy, nausea, headache and fever have occasionally been reported.
PRECAUTIONS: If sensitivity to test doses is manifested, the drug should not be given. Imferon (iron dextran injection) must be administered by deep intramuscular injection only. Inject only in the upper outer quadrant of the buttock, not in the arm or other exposed area.
CONTRAINDICATIONS: Imferon (iron dextran injection) is contraindicated in patients sensitive to iron dextran complex. Since its use is intended for the treatment of iron deficiency anemia only it is contraindicated in other anemias.
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BOOK REVIEWS

Community Mental Health Services in Northern Europe—Great Britain, Netherlands, Denmark, and Sweden. Sylvan S. Furman. Written under contract with the U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Institute of Mental Health, Bethesda, Md. Price, $1.75. Pp. 215. Washington, D. C.: U. S. Government Printing Office, 1966.

This book is a collection of sketches of about 50 mental health facilities in England, Scotland, Holland, Denmark, and Sweden visited by Mr. Furman over a 15-week period in 1963 and 1964. These sketches are usually cross-sectional, although sometimes the factors contributing to the selection of a model are stated and sometimes the results of treatment are given. The goals of these units are comprehensiveness and continuity of care of patients with psychiatric problems. Extensive coördination with general practitioners, willingness to make house calls, and pay-for-work therapy are mentioned again and again in describing the work at these community facilities.

A few of the more specialized units are described, such as Herstedvester's approach to sociopaths, Crowley's geriatric unit, the Elizabeth Frye Home for inadequate mothers, and Belmont (now Henderson) Hospital's therapeutic community which was started 19 years ago by Maxwell Jones.

This book may interest those who would like a brief and uncritical look at some psychiatric and social institutions in Europe. A selective use of the book as a reference is hindered by the lack of an index.

Roger Peele, M.D.

Current Pediatric Therapy 1966–1967. Sydney S. Gellis, M.D., and Benjamin M. Kagan, M.D., editors, and 286 contributors. Price, $17.50. Pp. 956. Philadelphia: Saunders, 1966.

"Current Pediatric Therapy 1966–67" is the second edition of the newest methods used by 288 authors in treating specific pediatric illnesses. Many of the authors are regarded as experts in their particular field of knowledge. Their approaches have been critically reviewed by the editors, and the result is an extremely helpful book for the practicing physician who cares for children.

This book is arranged by organ systems with specific disorders listed under each system. Additional sections on infectious diseases, nutrition, mental and emotional disturbances, allergy, accidents and emergencies, unclassified diseases—sarcoidosis and amyloidosis, and diseases peculiar to the newborn. A miscellaneous section, including anesthesia, parental and electrolyte fluid therapy, high fever and disorders associated with travel, and a roster of drugs are included. References to the pertinent literature are included with most but not all diseases described. This book deserves to be on the book shelf of everyone who treats children as a handy, easy reference.

Thomas E. Reichelderfer, M.D.

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Electrocardiography and Vectorcardiography—Instrumentation, Fundamentals, and Clinical Applications. Lawrence E. Lamb, M.D. Price, $17.00. Pp. 609, with 603 illustrations. Philadelphia: Saunders, 1965.

There have been, in the last decade, a number of books which deal with electrocardiography and vectorcardiography, but this book has dedicated 166 pages to the physics, volume conduction, leads, the normal electrocardiogram and vectorcardiograph with special reference to the physics involved.

There are numerous illustrations and this first section is excellent reading for the individual who is going to specialize in cardiography.

The chapter dealing with myocardial damage and coronary artery disease is well illustrated, but all cardiologists will not entirely agree with some of the opinions expressed.

This section is also profusely illustrated with special reference to the location of the electrode and the variations of the T wave. It pays very little attention to the Q wave.

His recommendations for serial electrocardiograms could well be taken.

His description and remarks regarding the exercise tolerance test (Master two-step) are well worth reading again. His precaution about giving this test at the first signal indicating angina or coronary heart disease is well taken.

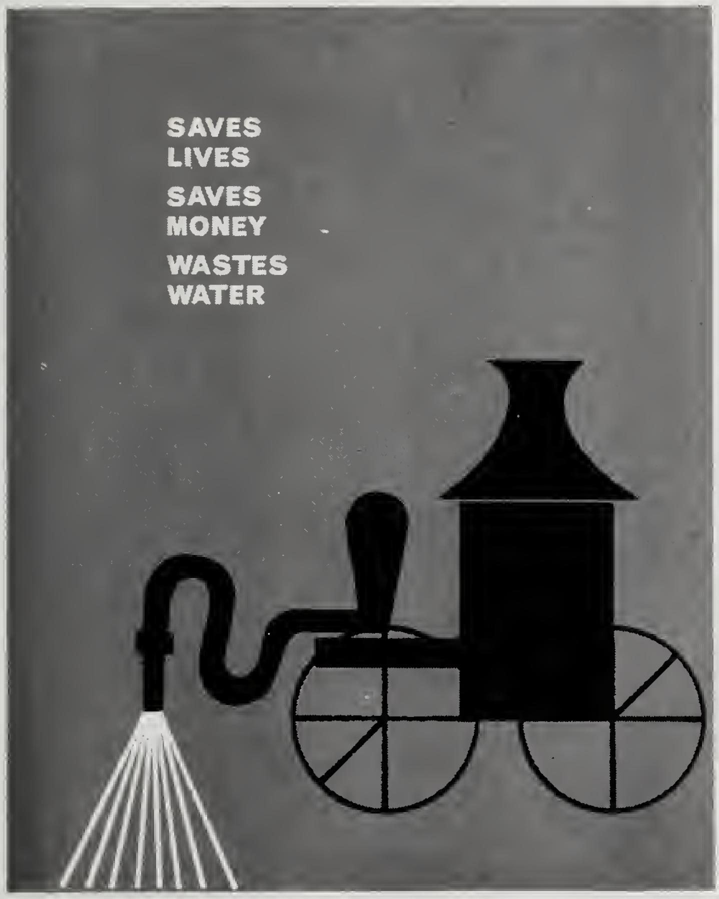
All in all, the book is profusely illustrated and is meant for the student who is preparing to specialize in cardiovascular disease. For the general practitioner it would have little appeal.

Paul F. Dickens, M.D.

Management of the Patient with Cancer. Edited by Thomas F. Nealon, Jr., M.D. With Contributions by 71 Authorities. Price, $27.50. Pp. 1067, illustrated. Philadelphia: Saunders, 1965.

This volume utilizes the services of 71 distinguished authors and clinicians in an attempt to clarify cancer management. These authorities do not agree com-

(*Continued on page 28*)



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Dosage: One 2 or 4 mg. tablet once or twice daily.

Precautions: As with all effective diuretics, vigorous therapy may produce electrolyte depletion. Patients with severely reduced renal function should be observed carefully since thiazides may be contraindicated. Care should be taken with patients predisposed to diabetes or gout. Patients with a tendency to potassium deficiency, as in hepatic cirrhosis or diarrheal syndromes, or those under therapy with digitalis, ACTH, or certain adrenal steroids, also should be watched carefully.

Side Effects: Nausea, flushing, constipation, skin rash, muscle cramps and gastric discomfort have occasionally been noted; rarely thrombocytopenia and bone marrow depression, photosensitivity, cholestatic jaundice, pancreatitis, perimacular edema, gout and diabetes have been caused by the administration of thiazides.

Contraindications: Complete renal shutdown; rising azotemia or development of hyperkalemia or acidosis in severe renal disease; demonstrated hypersensitivity.

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Book Reviews

(*Continued from page 26*)

pletely with each other; the reader will not agree with all.

Nevertheless, this volume presents a brief review of the past, a thorough discussion of the present, and a philosophical glimpse into the future of our common problem—cancer.

No single volume could completely cover this subject. The editor makes it clear that this was not his intent. Detailed surgical technique, radiological techniques, etc., were intentionally omitted. However, all known armamentaria, diagnostic and therapeutic, are discussed both in general chapters and under specific entities. The discussions of the basic problems of cancer philosophy are excellent. The presentation of the uses of chemotherapy is very complete without becoming so involved as to be interesting only to the oncologist. Each chapter on a specific disease is of interest, whether it be on the common cancer of the breast or the uncommon cancer of the parathyroid.

The discussion on rates of growth and "doubling time," and their effect on the prognosis of the disease, as well as their effect on the concept of biologic predeterminism, is clearly presented. The shortcomings of evaluating results based on comparison of groups of patients not really comparable are adequately illustrated. In addition, it is shown that the simple survival rate is an incomplete evaluation of a method of treatment. Many excellent photographs and charts are utilized throughout the volume.

Epicharmus said, "The wise man must be wise before, not after, the event." It would be wise for every physician who endeavors to treat, or designates another to treat, cancer to have this volume. Certainly it belongs in every hospital library.

James E. Boland, M.D.

Ciba Foundation Symposium: Cellular Injury. Edited by A. V. S. de Reuck, M.Sc., D.I.C., A.R.C.S., and Julie Knight, B.A. Price, $12.00. Pp. 403, with 81 illustrations. Boston: Little, 1964.

Today there is an increasing emphasis placed on continuing education for doctors, including the area of the Basic Sciences. This little volume is very interesting and should provide not only valuable information but also satisfaction to those who read and study for their own interest in and curiosity about Basic Science developments. It will also aid those responsible for planning and supervising programs related to Basic Science in medicine and surgery.

The volume, entitled "Cellular Injury," while it comprises 403 pages, is compact and is divided into 15 chapters or separate presentations. As is the custom with a Ciba Foundation Symposium, the various subjects are brief and are concisely presented by experts. They are enhanced by the inclusion of (1) appropriate charts, tables, photographs and diagrams, as well as (2) a brief bibliography, and (3) a question-and-answer discussion, which may include questions the reader had in mind, or may bring out weakness in the work or supplement it.

One of the more satisfying aspects of the reports is the intelligent effort throughout to correlate cellular function with structure. This is no snobbish work praising biochemical and physiological activity only, for highly refined chemical studies are correlated with morphological changes observed with the electron microscope, phase-contrast microscopy, and microcinematography and fluorescent microscopy.

There are excellent presentations on the role of biological alkylating agents, the action of dead cells on living cells (infarcts and inflammation), the mechanism of action of folic acid antagonist and corticosteroids, ion shifts, dietary deficiencies and lipids, as well as the role of membranes. In addition to the actions of exogenous and endogenous agents, viruses are also evaluated and matters such as age are considered.

This book, though entitled "Cellular Injury," may have gained a degree of fascination had it been entitled "Mechanisms and Stages of Cell Death." Through it you are in attendance at an outstanding symposium on the basic science of cellular injury. Any takers?

George P. Blundell, M.D.

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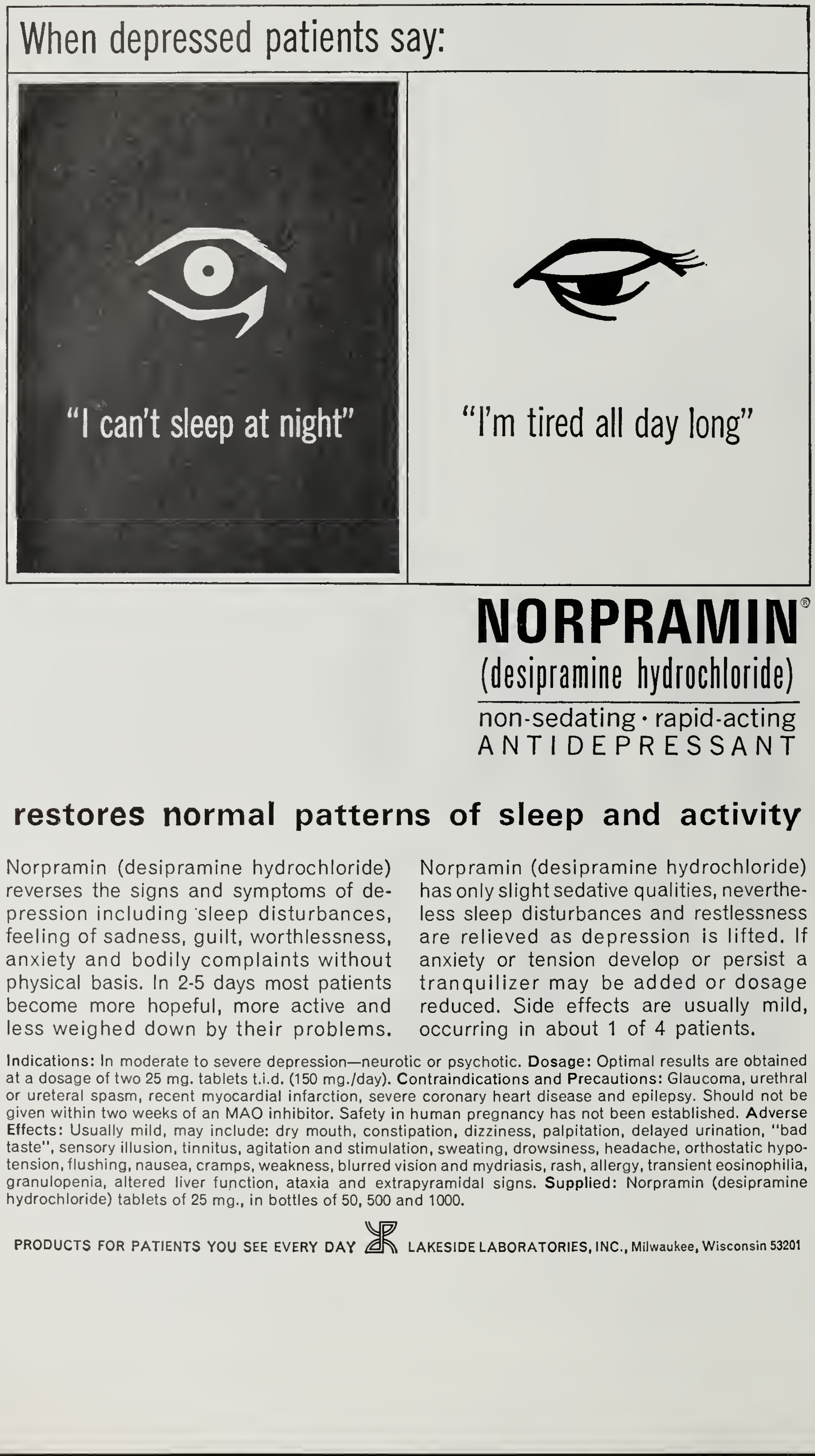

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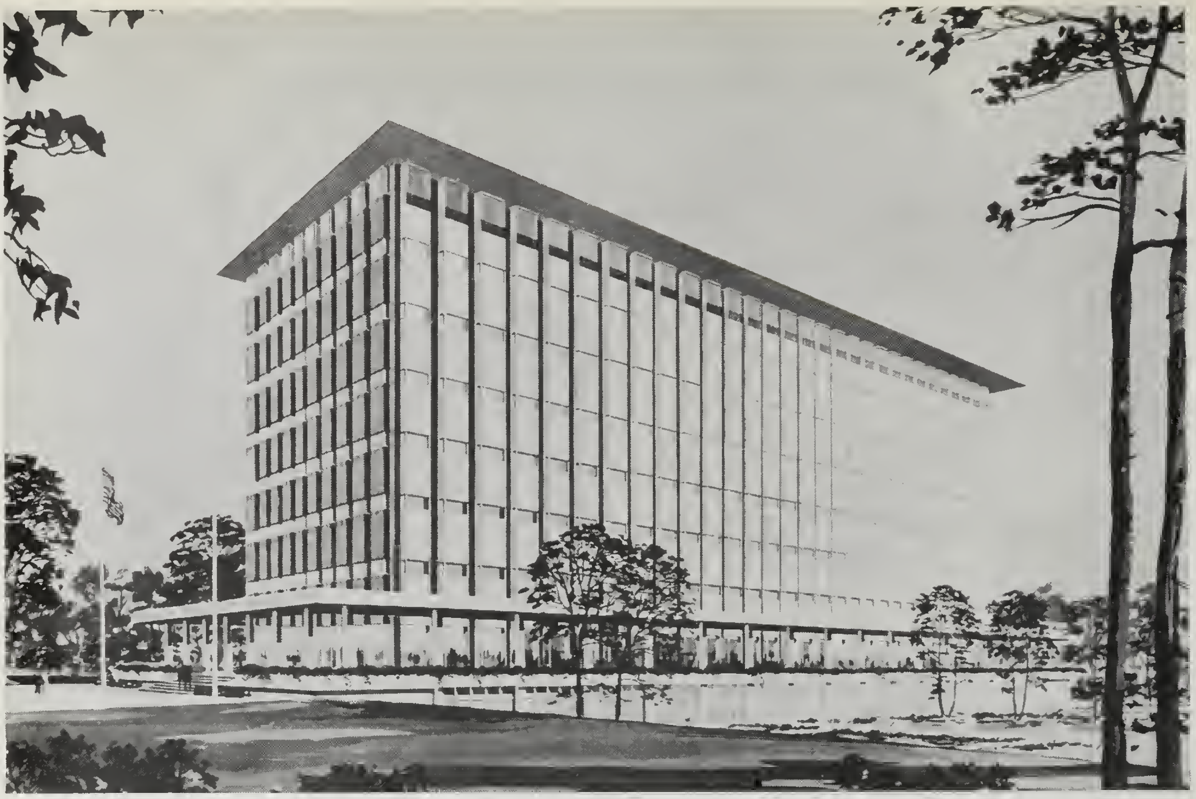

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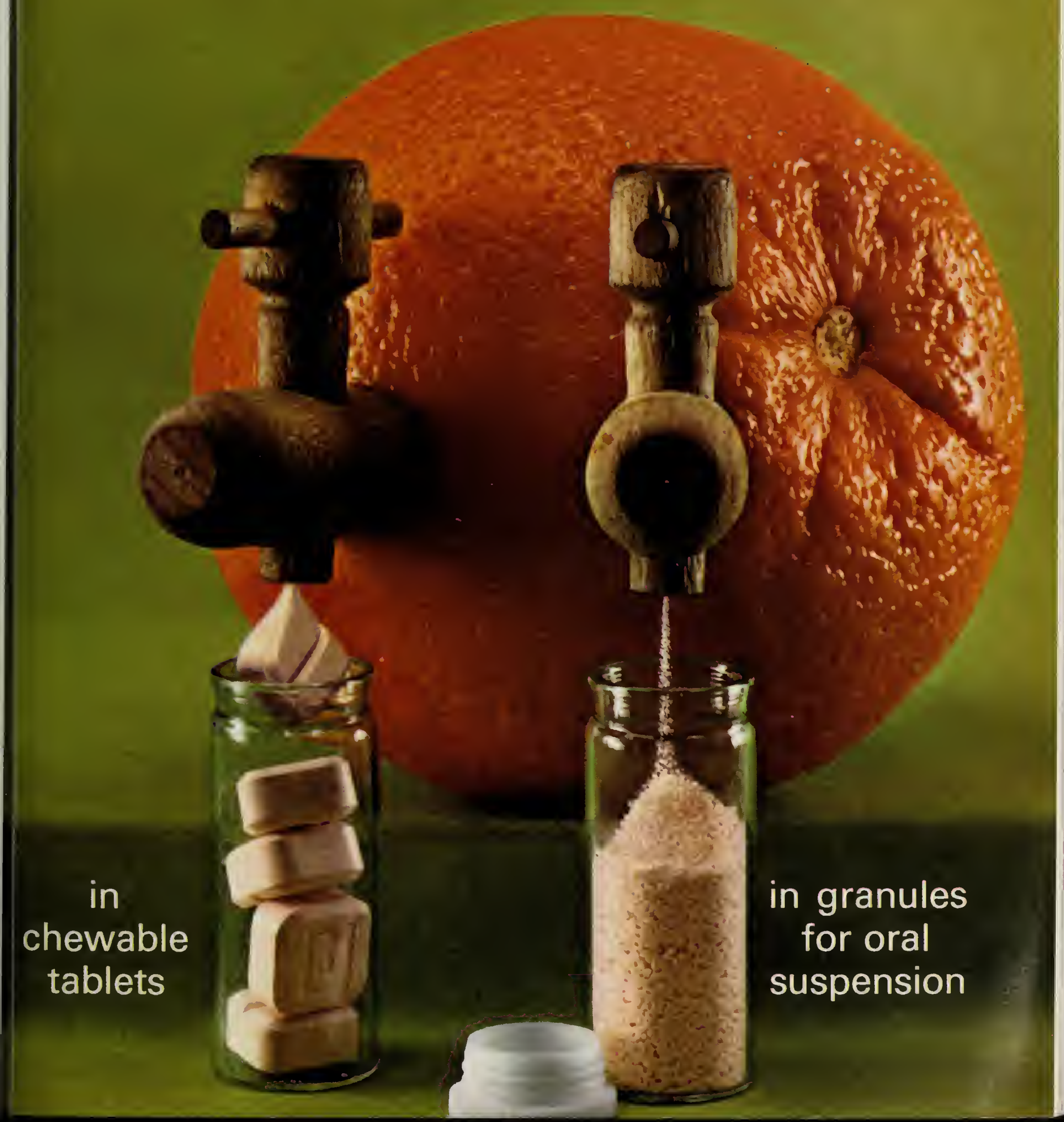
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Warnings: As with other forms of sulfonamide therapy, carefully evaluate patients with liver or kidney damage, urinary obstruction, or blood dyscrasia. Deaths have been reported from hypersensitivity reactions and blood dyscrasias following use of sulfonamides. Perform blood counts and liver and kidney function tests if used repeatedly at close intervals or for long periods.

Precautions: Use sulfonamides with caution in patients with a history of allergy. Assure adequate fluid intake to prevent crystalluria and institute alkali therapy if indicated.

Adverse Reactions: Sulfonamide therapy may be associated with headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, injection of the conjunctiva and sclera, petechiae, purpura, hematuria and crystalluria.

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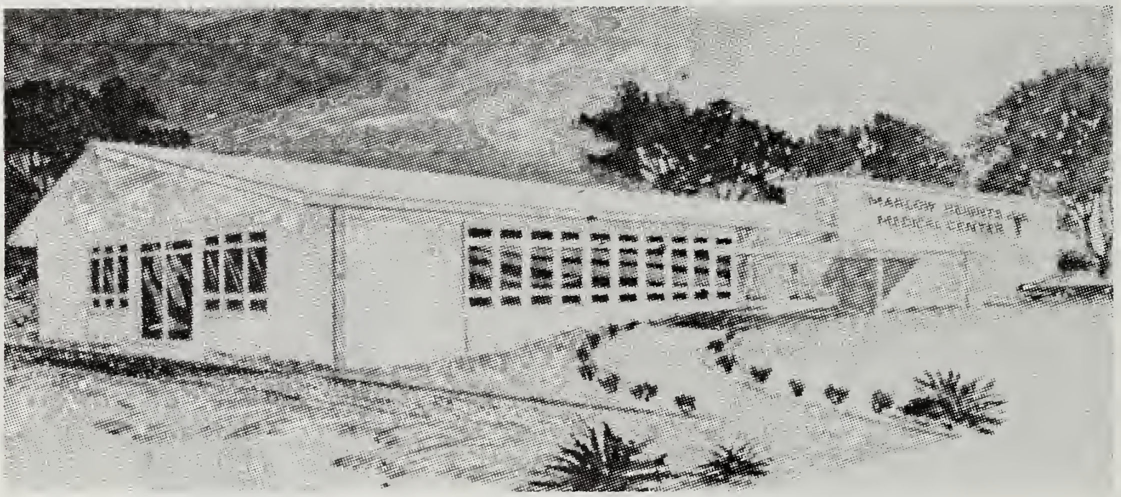

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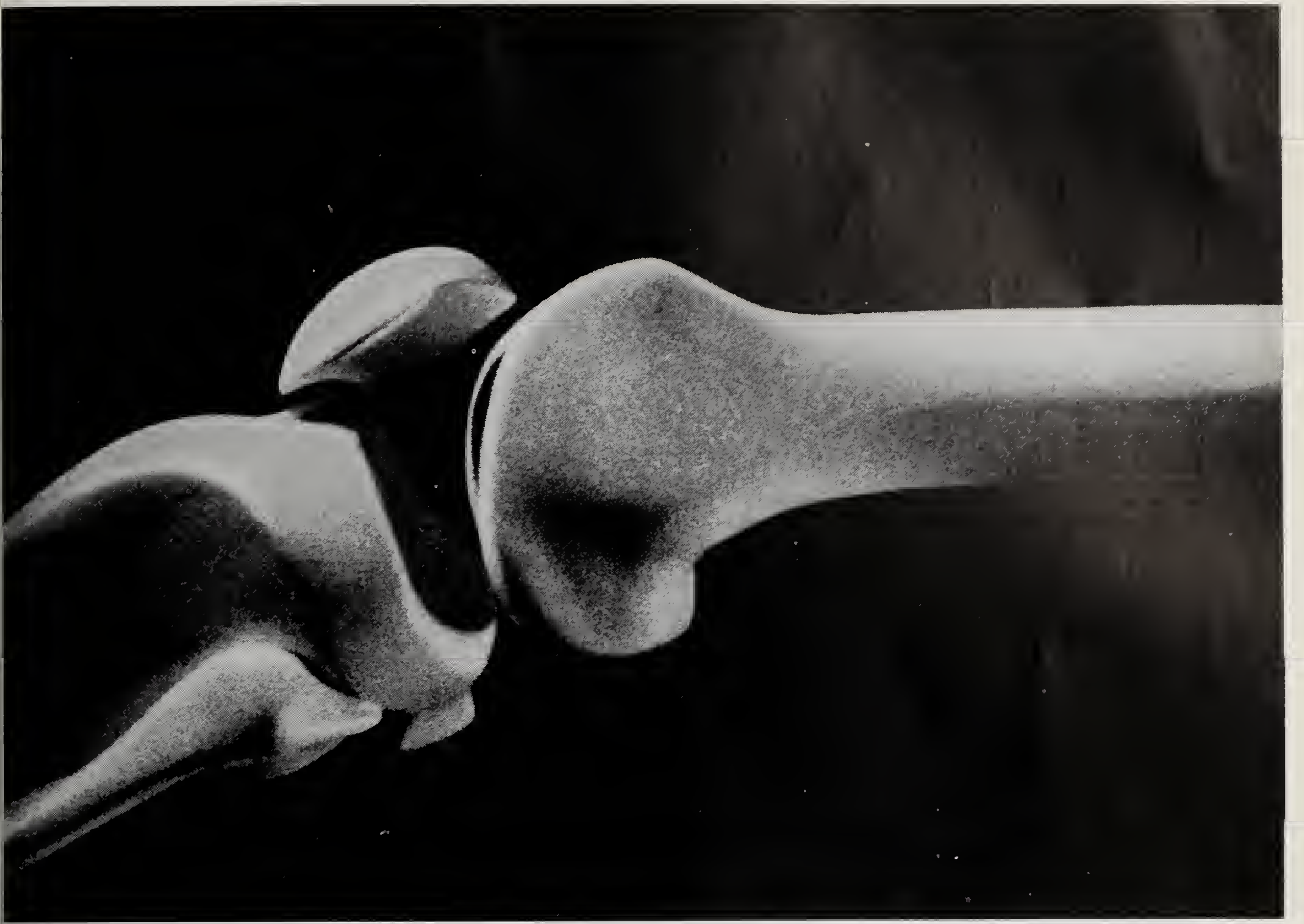

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Precautions
Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Make regular blood counts. Use greater care in the elderly.

Warning
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Adverse Reactions
The most common are nausea, edema and drug rash. Hemodilution may cause moderate fall in red cell count. The drug may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, generalized allergic reaction, stomatitis, salivary gland enlargement, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

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NATIONAL AND REGIONAL MEETINGS

August 8–12: 71st Annual Session of National Medical Association. Pick-Congress Hotel, Chicago. Address: Dr. John T. Givens, *Executive Secretary*, 2400 Corprew Avenue, Norfolk, Va.

August 12–14: International Doctors in Alcoholics Anonymous. Speedway Motel, Indianapolis, Ind. Address: Convention Committee, 5842 North LaSalle Avenue, Indianapolis, Ind.

August 25–27: West Virginia State Medical Association. The Greenbrier, White Sulphur Springs, West Va. Address: Mr. William H. Lively, *Executive Secretary*, 401 Atlas Bldg., 1031 Quarrier Street, Charleston, West Va. 25324.

September 8–10: American Association of Obstetricians and Gynecologists. The Homestead, Hot Springs, Va. Address: Dr. Robert B. Wilson, *Executive Secretary*, 200 First Street, S.W., Rochester, Minn. 55902.

September 9: Medical and Chirurgical Faculty of the State of Maryland. Ocean City, Md. Address: Mr. John Sargeant, *Executive Secretary*, 1211 Cathedral Street, Baltimore, Md. 21201.

September 11–12: Congress on Medical Socio-Economics. Palmer House, Chicago. Address: Dr. Charles Edwards, Department of Socio-Economic Activities, AMA, 535 North Dearborn Street, Chicago, Ill. 60610.

September 16–24: American Society of Clinical Pathologists. Washington Hilton Hotel, Washington. Address: Miss Martha Damron, Administrative Secretary, 445 North Lake Shore Drive, Chicago, Ill. 60611.

September 17–23: College of American Pathologists. Washington Hilton Hotel, Washington. Address: Mr. Oliver J. Neibel, Jr., Administrative Secretary, 230 North Michigan Avenue, Chicago, Ill. 60601.

September 25–30: III International Congress of Nephrology. Washington Hilton Hotel, Washington. Address: Secretariat, III International Congress of Nephrology, 9650 Wisconsin Avenue, Washington, D. C. 20014.

September 29–October 2: American Medical Writers' Association. Waldorf Astoria, New York. Address: Mr. James E. Bryan, *Executive Director*, 2000 P Street, N.W., Washington, D. C. 20036.

October 7–8: Congress on Medical Quackery. Pick-Congress Hotel, Chicago. Address: Dr. John G. Thomsen, *Chairman*, American Medical Association, Committee on Quackery, 535 North Dearborn Street, Chicago, Ill. 60610.

October 7–14: American Academy of General Practice. War Memorial, Boston, Mass. Address: Mr. Mac F. Cahal, *Executive Director*, Volker Blvd. at Brookside, Kansas City, Mo. 64112.

October 23–26: American College of Gastroenterology. Bellevue-Stratford Hotel, Philadelphia. Address: Mr. Daniel Weiss, *Executive Director*, 33 West 60th Street, New York, N. Y. 10023.

November 14–17: Southern Medical Association. Washington Hilton Hotel, Washington. Address: Mr. Robert F. Butts, 2601 Highland Avenue, Birmingham, Ala. 35205.

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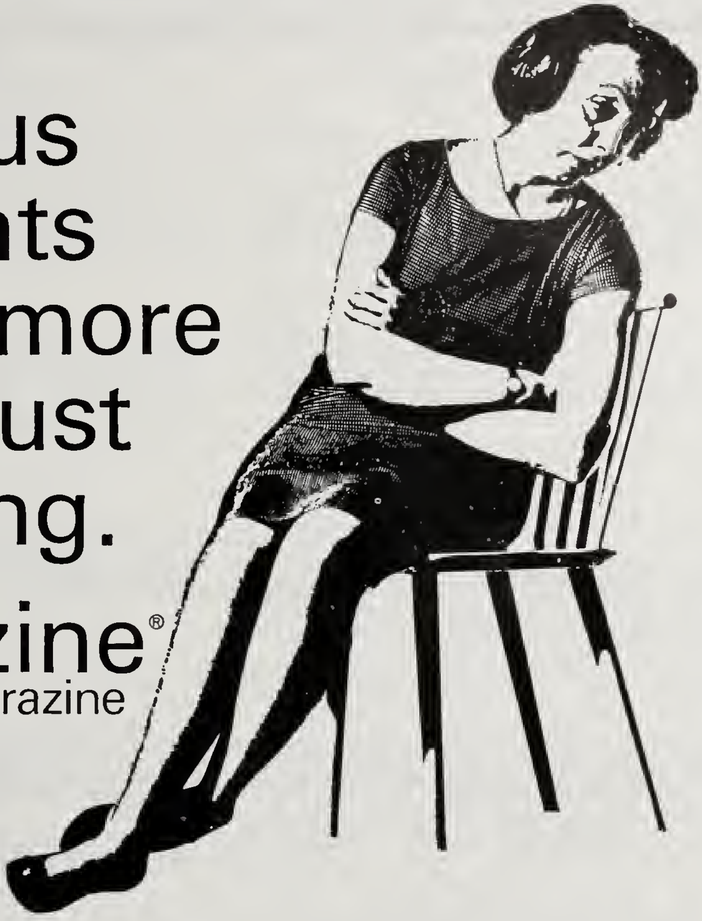

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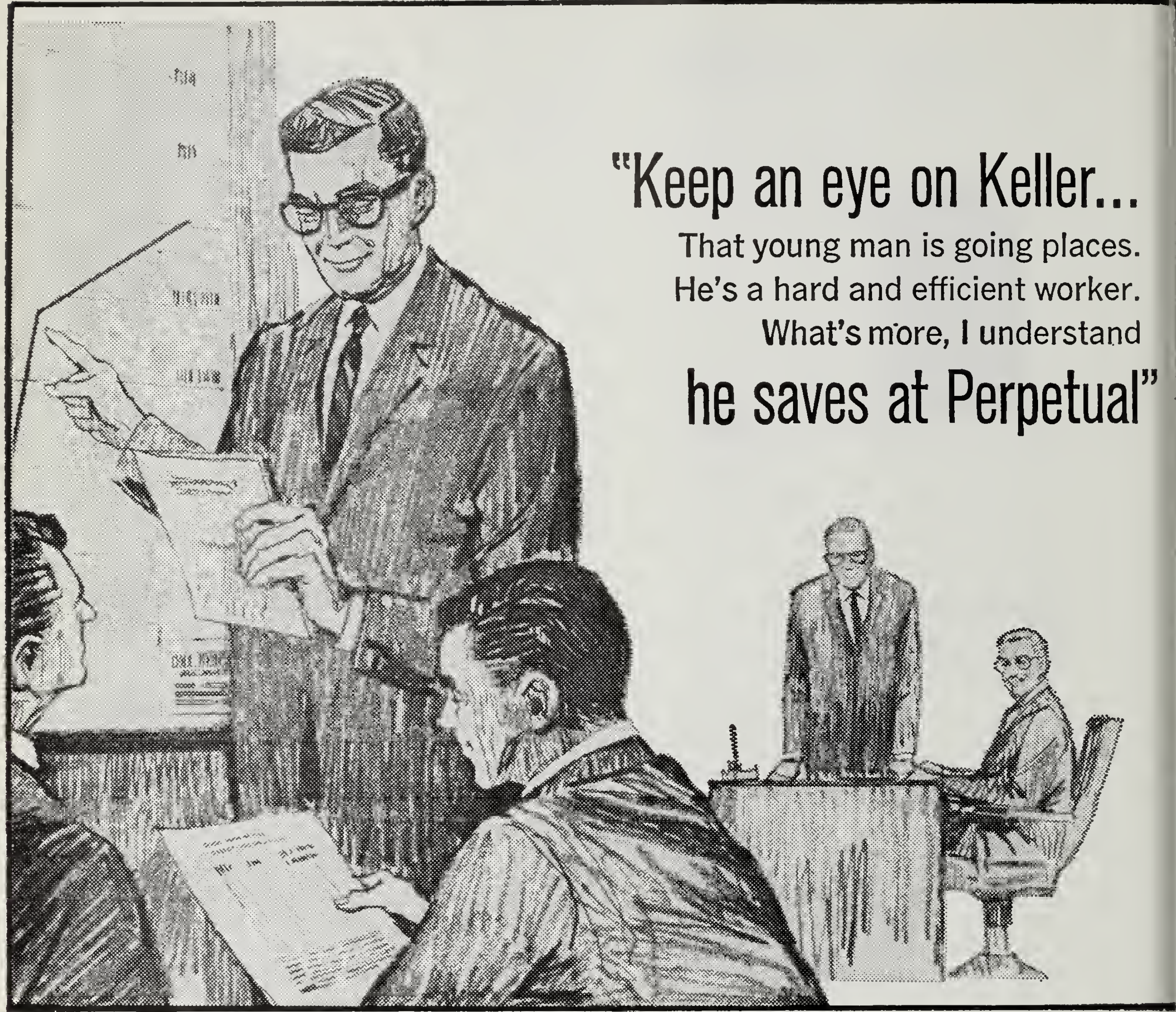
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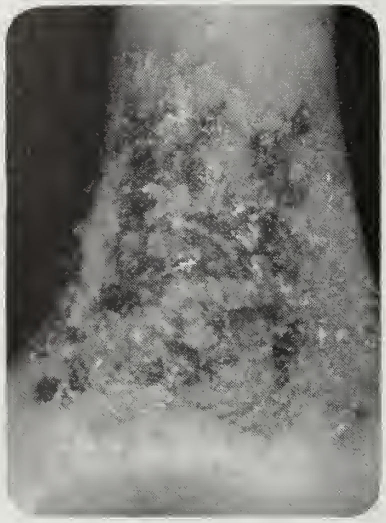
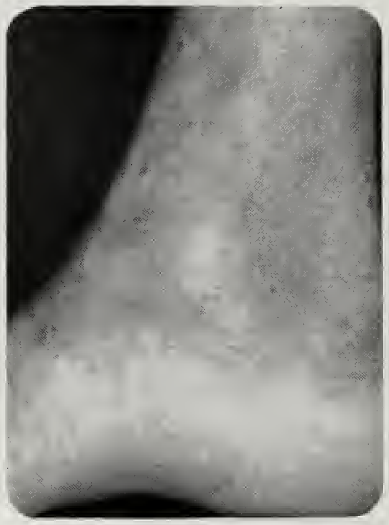
eczema: scourge of childhood



R. R., Age 11—Before treatment—
atopic eczema of long standing



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to :

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Washington, D. C.

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Side Effects: Side effects, usually dose related, include drowsiness, ataxia, minor skin rashes, edema, menstrual irregularities, nausea and constipation. When treatment is protracted, blood counts and liver function tests are advisable. Paradoxical reactions may occasionally occur in psychiatric patients. Individual maintenance dosages should be determined.
Precautions: Advise patients against possibly hazardous procedures until maintenance dosage is established. Though compatible with most drugs, use care in combining with other psychotropics, particularly MAO inhibitors or phenothiazines; warn patients of possible combined effects with alcohol. Observe usual precautions in impaired renal or hepatic function, in long-term treatment and in presence of depression or suicidal tendencies. Exercise caution in administering drug to addiction-prone patients or those who might increase dosage; withdrawal symptoms, similar to those seen with barbiturates or meprobamate, can occur upon abrupt cessation after prolonged overdosage. Caution should be exercised in prescribing any therapeutic agent for pregnant patients.
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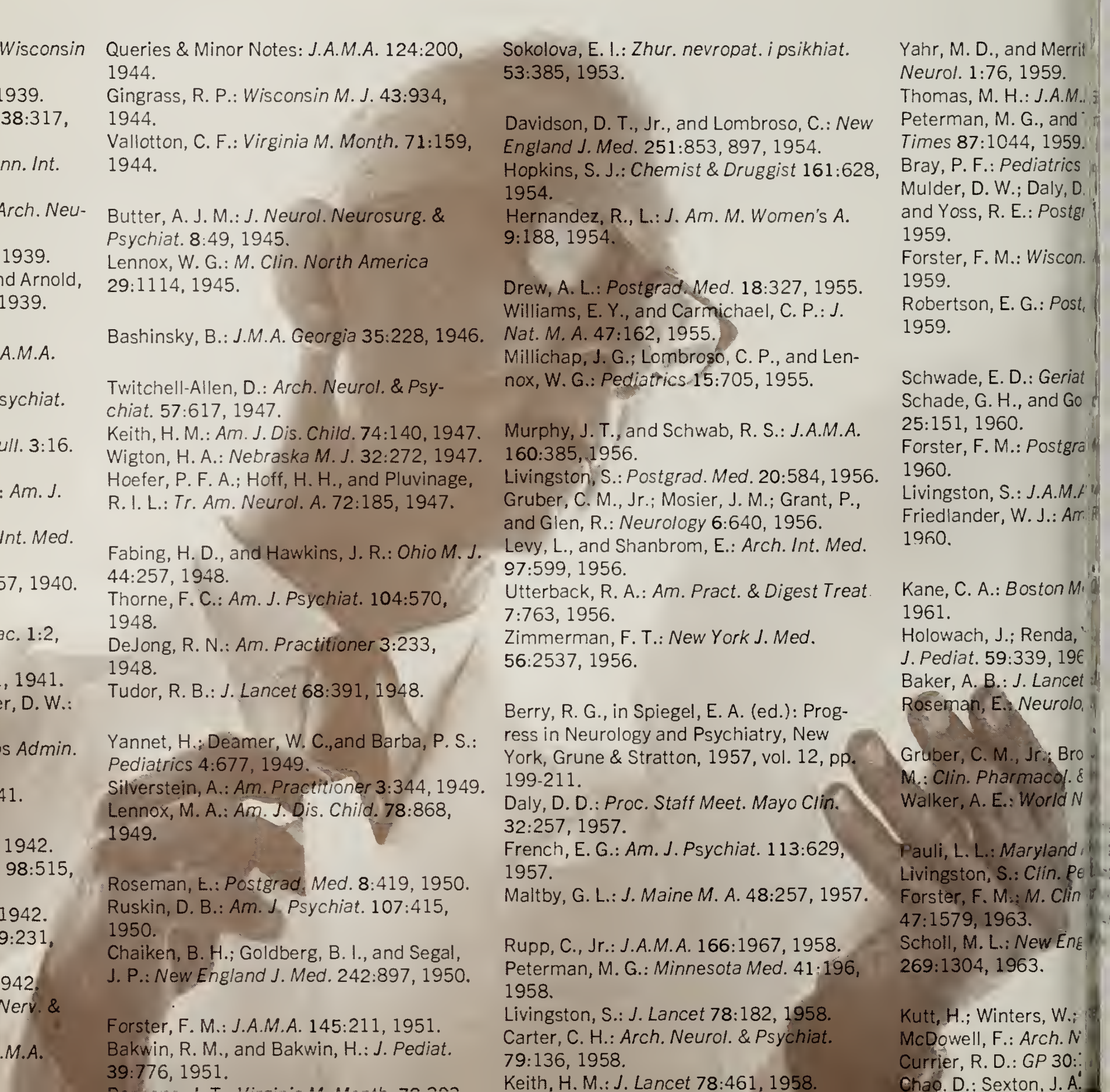

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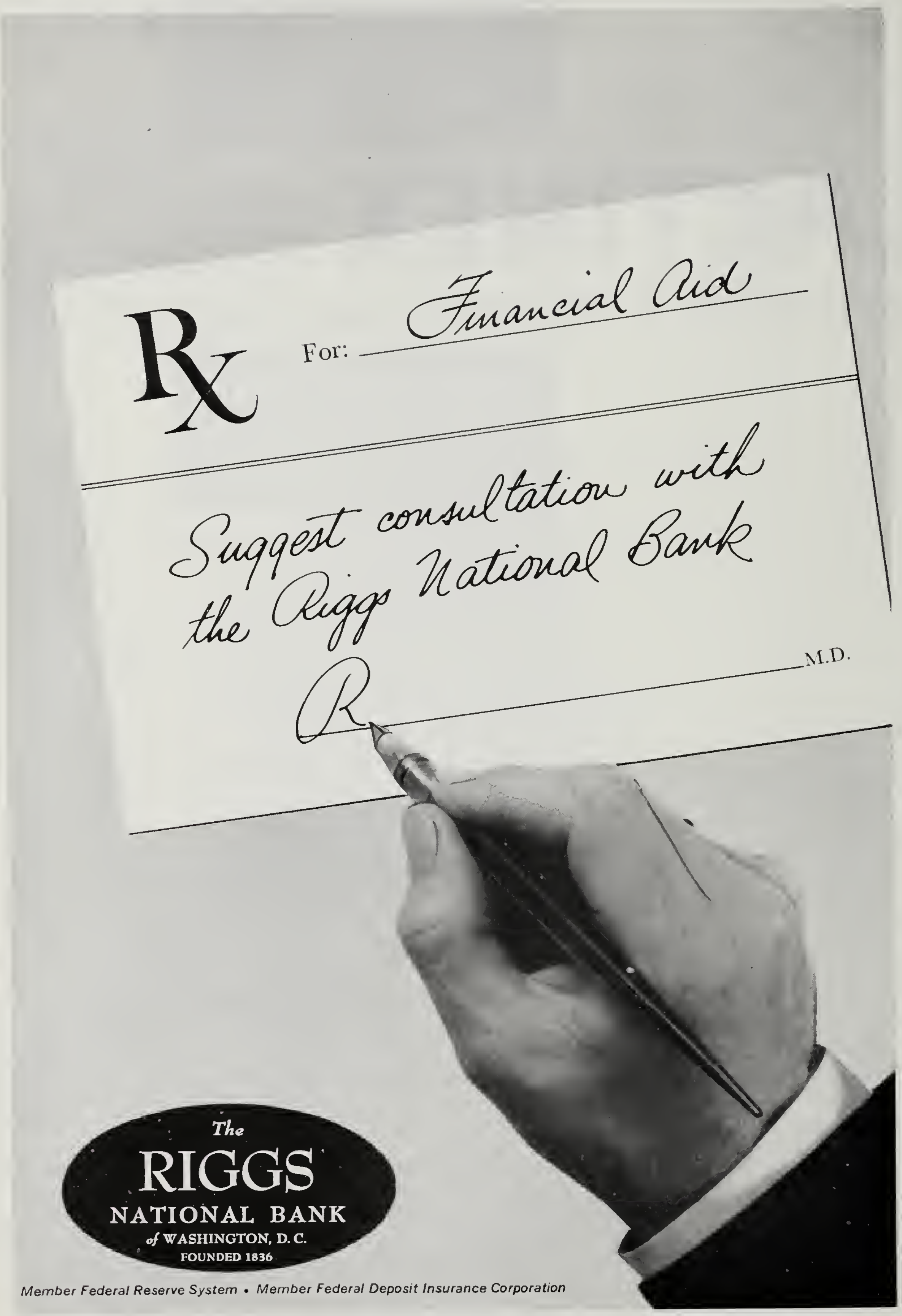
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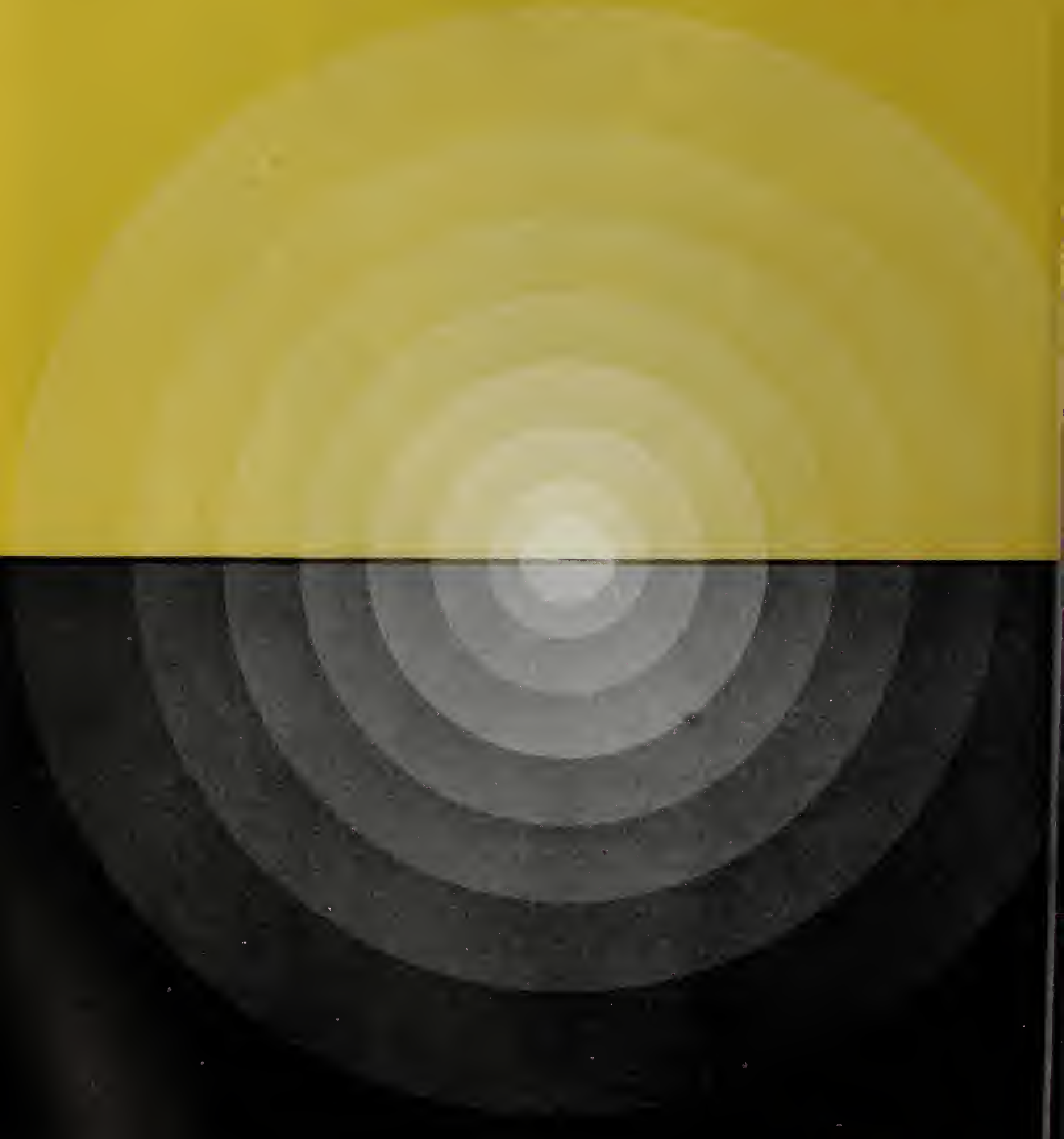

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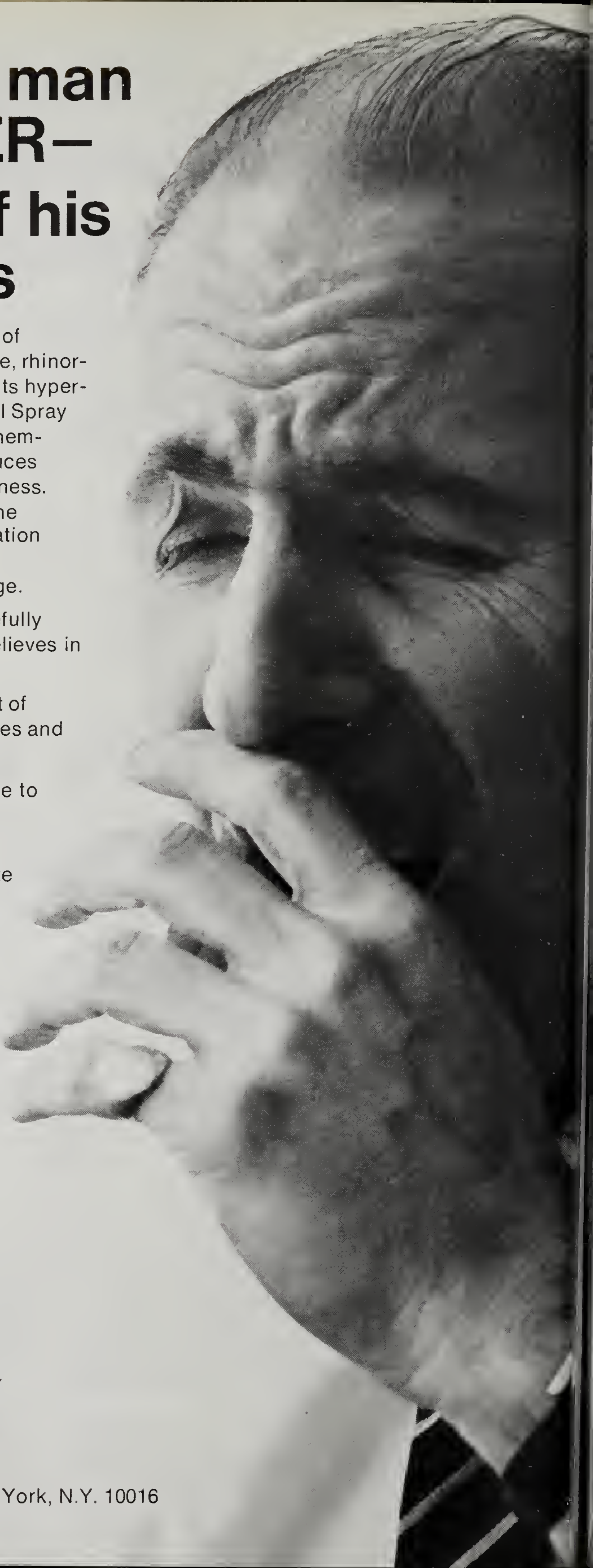

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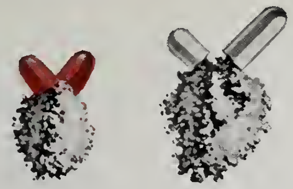

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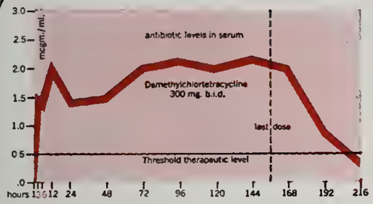

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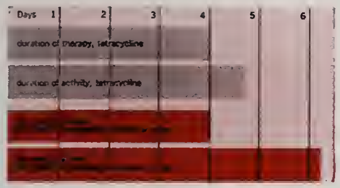

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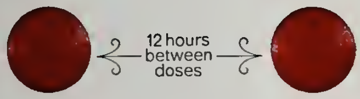

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eenhouse, H. R.: Med. Times 91:1069, November, 1963.

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polla, A.: Clin. Med. 8:1332, July, 1961.

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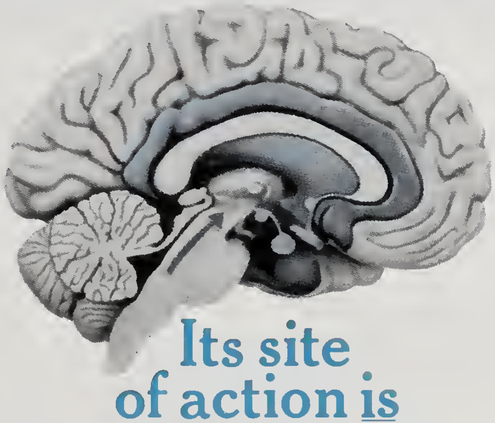

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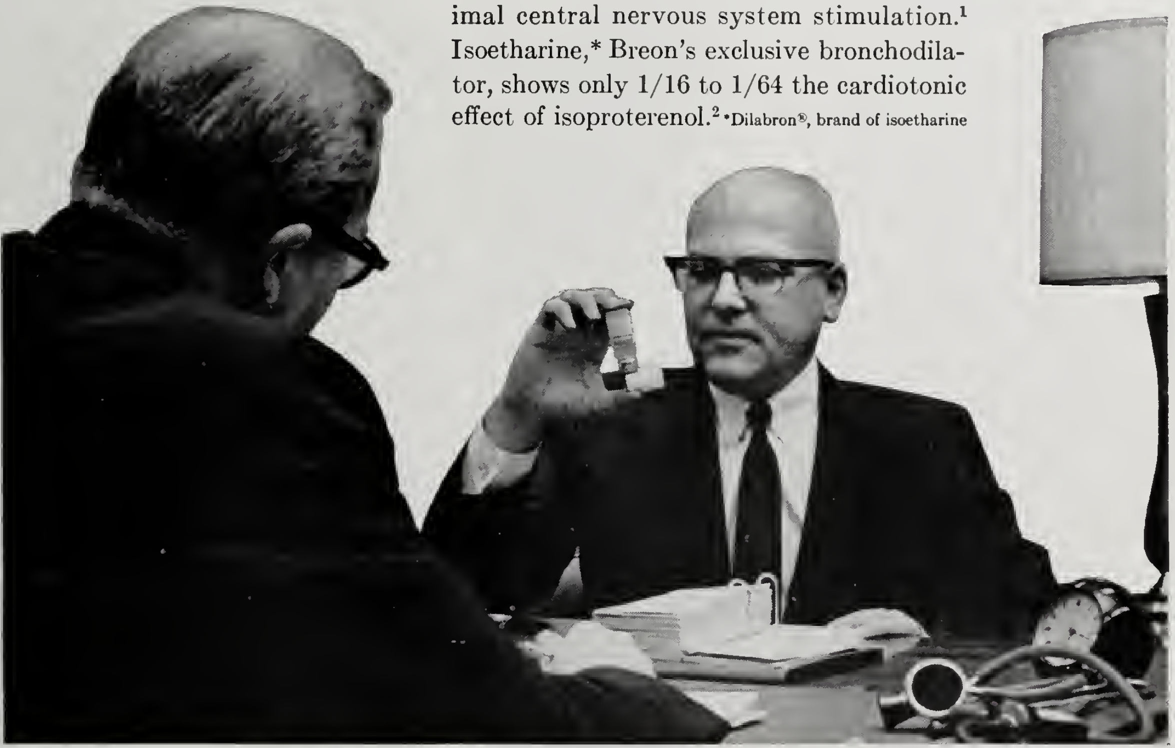

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Advantage: Both components of Regroton are long-acting.
Average dosage: One tablet daily with breakfast.
Contraindications: History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.
Warning: Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs. With administration of enteric-coated potassium supplements, the possibility of small bowel lesions should be kept in mind.
Precautions: Reduce dosage of concomitant antihypertensive agents by one-half. Discontinue if the BUN rises or liver dysfunction is aggravated. Electrolyte imbalance and potassium depletion may occur; take particular care in cirrhosis or severe ischemic heart disease, and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use with caution in patients with ulcerative colitis, gallstones, or bronchial asthma.
Side effects: Nausea, vomiting, diarrhea, muscle cramps, headaches and dizziness. Potential side effects include angina pectoris, anxiety, depression, drowsiness, hyperglycemia, hyperuricemia, lassitude, leukopenia, nasal stuffiness, nightmare, purpura, urticaria, and weakness.
For full details, see the complete prescribing information.
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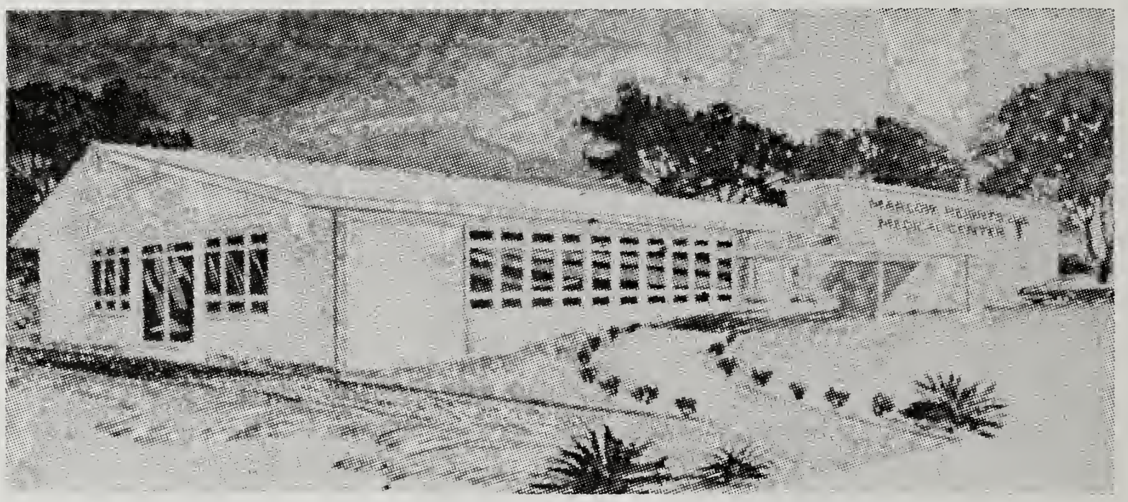

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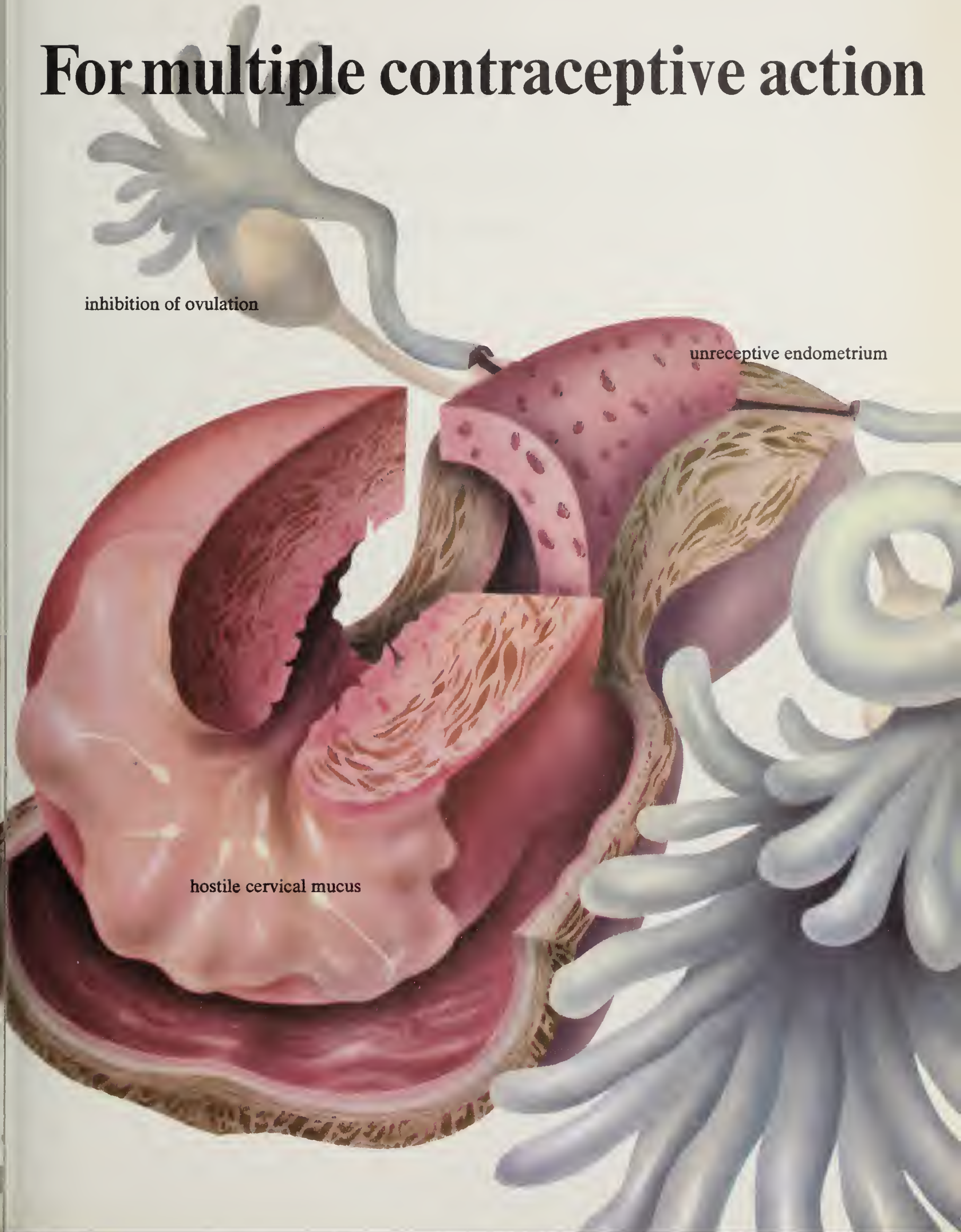
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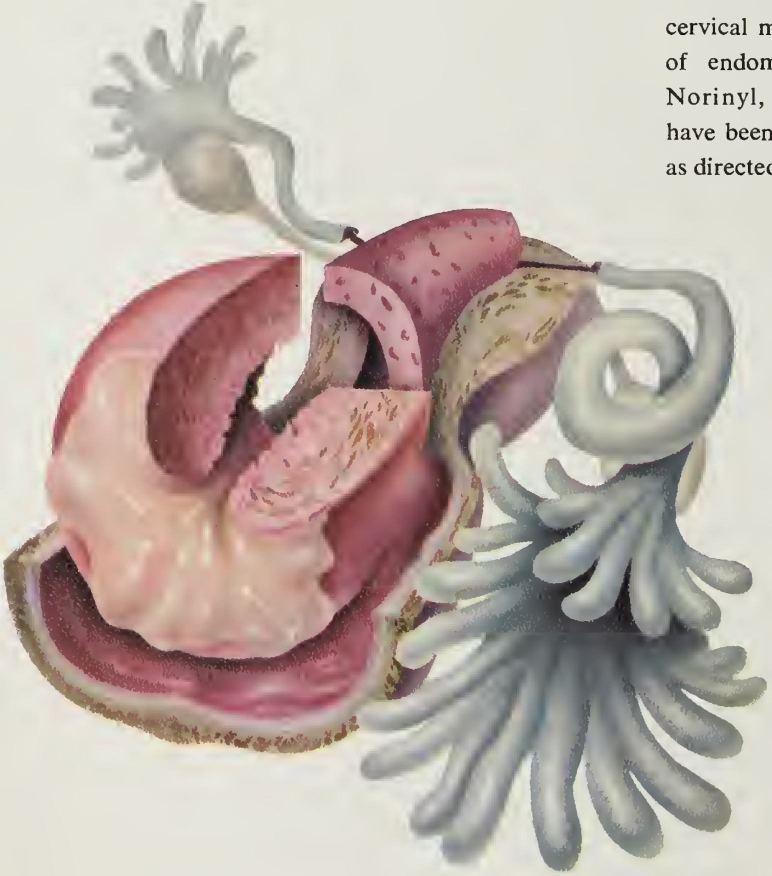
no unplanned pregnancies

Norinyl provides multiple action for maximum assurance of success. It does not depend on ovulation inhibition alone for contraceptive effectiveness. The mechanism of action of combined hormonal therapy results in ovulation inhibition reinforced by other protective mechanisms, including a hostile cervical mucus[1-13] and an acceleration of endometrial changes.[1-3,7-16] With Norinyl, no unplanned pregnancies have been reported to date when used as directed.



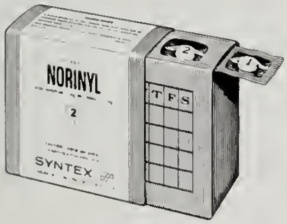
plus important supportive benefits that help her through those critical early months of oral contraception

low incidence of side effects

Low incidence of BTB and spotting, nausea and amenorrhea tends to minimize side effect problems and increases patient cooperation.

no confusion about dosage

An unbreakable "confusionproof" package makes it easy to adhere to prescribed dosage schedule: individually sealed tablets numbered from 1 through 20 *plus* monthly calendar record enables patient to double-check dosage intake by day and corresponding tablet number.



Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: **1.** Council on Drugs JAMA 187·664 (Feb. 29) 1964. **2.** Bryans, F. E.: Canad Med Ass J 92·287 (Feb. 6) 1965. **3.** Goldzieher, J. W.· Med Clin N Amer 48:529 (Mar.) 1964 **4.** Cohen, M. R.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965. **5.** Hammond, D. O.: Ibid. **6.** Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A · Fertil Steril 14:402 (Jul.-Aug.) 1963. **7.** Goldzieher, J. W , Moses, L. E , and Ellis, L. T.: JAMA 180:359 (May 5) 1962 **8.** Kempers, R. D : GP 29:88 (Jan.) 1964 **9.** Tyler, E. T.: JAMA 187·562 (Feb. 22) 1964. **10.** Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M Fertil Steril 16·158 (Mar.-Apr.) 1965. **11.** Flowers, C. E., Jr · N Carolina Med J 25:139 (Apr.) 1964. **12.** Goldzieher, J. W.: Appl Ther 6:503 (June) 1964. **13.** The Control of Fertility. Report adopted by the Committee on Human Reproduction of the American Medical Association. JAMA 194·462 (Oct. 25) 1965. **14.** Flowers, C E., Jr : JAMA 188:1115 (June 29) 1964. **15.** Merritt, R. I.: Appl Ther 6:427 (May) 1964. **16.** Newland, D. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

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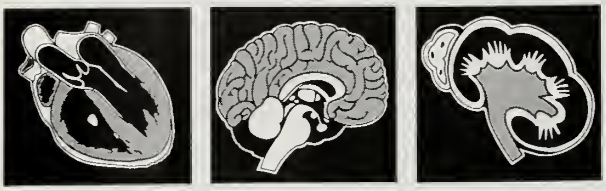
SQUIBB NOTES ON THERAPY

Behind continued high blood pressure readings lies the possibility of organic damage[1-13]

MANY OF THE aspects of essential hypertension are unpredictable—either because there are a number of mechanisms involved or because individuals differ in their responses to these mechanisms.[1]

There is one aspect of hypertension, however, that seems, in many cases, predictable. ". . . when the blood pressure is elevated to a marked degree for an adequate period of time, this in itself leads to perpetuation of the syndrome with resulting vascular damage throughout the body."[14] All too often the disease progresses until there is damage to one of three vital organs: the heart, the kidney, the brain.



> "Hypertension is certainly a major factor in the genesis of coronary heart disease, and it is even more important when compounded with obesity."[4]
>
> "[Vascular deterioration] can be clearly seen in the kidney with a degree of damage that can be measured by renal function studies."[10]

". . . most evidence suggests that reduction of blood pressure, when it is too high, not only relieves the heart of excess work but reduces vascular damage."[1]

"In short, treatment is indicated."[1]

Antihypertensive therapy will not restore the blood vessels to normal. Yet many of the vascular changes and symptoms caused by increased blood pressure may be arrested or alleviated when the blood pressure is reduced to normotensive levels.[7]

Reducing the blood pressure helps curtail further vascular damage and improves the prognosis — when damage is not too far advanced before therapy is started.[14] Essential hypertension is an indication not only for treatment, but for *early* and adequate treatment of the patient in question.

Reduce the blood pressure with Rautrax-N

Rautrax-N combines the antihypertensive-tranquilizing action of whole root rauwolfia with the antihypertensive-diuretic action of bendroflumethiazide in one convenient medication. The two drugs complement each other so that smaller doses of both are possible.

Rauwolfia combined with bendroflumethiazide is particularly effective in long-term therapy,[15-17] since beneficial effects do not diminish with continuous daily administration.

For most patients 1 or 2 Rautrax-N tablets daily are sufficient for maintenance therapy. The simplicity, convenience and economy of such a dosage schedule are of particular benefit to older patients.

References: 1. Page, I. H., and Dustan, H. P.: The Usefulness of Drugs in the Treatment of Hypertension, in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 95. **2.** Hollander, W.: The Evaluation of Antihypertensive Therapy of Essential Hypertension in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 97. **3.** Nickerson, M.: Antihypertensive Agents and the Drug Therapy of Hypertension, in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Co., 1965, p. 727. **4.** Berkson, D. M.: Indust. Med. & Surg. **32**:371, 1963. **5.** Cohen, B. M.: M. Times **91**:645, 1963. **6.** Lee, R. E., et al.: Am. J. Cardiol. **11**:738, 1963. **7.** Moyer, J. H.: Am. J. Cardiol. **9**:821, 1962. **8.** Moser, M.: New York J. Med. **62**:1177, 1962. **9.** Wood, J. E., and Battey, L. L.: Am. J. Cardiol. **9**:675, 1962. **10.** Moyer, J. H., and Heider, C.: Am. J. Cardiol. **9**:920, 1962. **11.** Moser, M., and Macaulay, A. I.: New York State J. Med. **60**:2679, 1960. **12.** Judson, W. E.: Nebraska M. J. **44**:305, 1959. **13.** Hodge, J. V.; McQueen, E. G., and Smirk, H.: Brit. M. J. **1**:5218, 1961. **14.** Moyer, J. H., and Brest, A. N.: Hypertension Recent Advances, Philadelphia, Lea & Febiger, 1961, p. 633. **15.** Berry, R. L., and Bray, H. P.: J. Am. Geriatrics Soc. **10**:516, 1962. **16.** Reid, W. J.: J. Am. Geriatrics Soc. **13**:365, 1965. **17.** Feldman, L. H.: North Carolina M. J. **23**:248, 1962.

Contraindications: Severe renal impairment or previous hypersensitivity. **Warning:** Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting or G.I. bleeding occur.

Precautions and Side Effects: The dose of ganglionic blocking agents, veratrum or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Caution is indicated in patients with depression, suicidal tendencies, peptic ulcer; electrolyte disturbances are possible in cirrhotic or digitalized patients. Marked hypotension during surgery is possible; consider discontinuing two weeks prior to elective surgery and observe patients closely during emergency surgery. Rauwolfia preparations may cause reversible extrapyramidal symptoms and emotional depression, diarrhea, weight gain, edema, drowsiness may occur. Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients, and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, rashes may occur.

Dosage and Supply: Initial dosage, 1 to 4 tablets daily, preferably at mealtime. Maintenance, 1 or 2 tablets daily. Rautrax-N is supplied as capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin®), 4 mg. bendroflumethiazide (Naturetin®), 400 mg. potassium chloride.

Also available: Rautrax-N Modified — capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin), 2 mg. bendroflumethiazide (Naturetin), 400 mg. potassium chloride. Both potencies available in bottles of 100. For full information, see Product Brief.

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Precautions: 'Soma', like other central nervous system depressants, should be used with caution in patients with known propensity for taking excessive quantities of drugs and in patients with known sensitivity to compounds of similar chemical structure, e.g., meprobamate.

Side Effects: The only side effect reported with any frequency is sleepiness, usually on higher than recommended doses. An occasional patient may not tolerate carisoprodol because of an individual reaction, such as a sensation of weakness. Other rarely observed reactions have included dizziness, ataxia, tremor, agitation, irritability, headache, increase in eosinophil count, flushing of face, and gastrointestinal symptoms.

One instance each of pancytopenia and leukopenia, occurring when carisoprodol was administered with other drugs, has been reported, as has an instance of fixed drug eruption with carisoprodol and subsequent cross reaction to meprobamate. Rare allergic reactions, usually mild, have included one case each of anaphylactoid reaction with mild shock and angioneurotic edema with respiratory difficulty, both reversed with appropriate therapy. In cases of allergic or hypersensitivity reactions, carisoprodol should be discontinued and appropriate therapy initiated. Suicidal attempts may produce coma and/or mild shock and respiratory depression.

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BOOKS RECEIVED

Acknowledgment is made of the following books which have recently been received.

Pathology, 5th ed., in 2 volumes. Edited by W. A. D. Anderson, M.A., M.D., F.A.C.P., F.C.A.P. Price per set, $21.00. Pp. 1439, with 1260 illustrations and 7 color plates. St. Louis: Mosby, 1966.

Current Diagnosis: A Biennial Volume of Clinical Diagnostic Methods and Evaluations. Edited by Howard F. Conn, M.D., Robert J. Clohecy, M.D., and Rex B. Conn, Jr., M.D. Price, $19.00. Pp. 843, illustrated. Philadelphia: Saunders, 1966.

An Atlas of Fine Structure. The Cell. Its Organelles and Inclusions. Don W. Fawcett, M.D. Price, $11.00. Pp. 448, with 240 figures. Philadelphia: Saunders, 1966.

Synopsis of Obstetrics, 7th ed. Charles E. McLennan, M.D. Price, $6.85. Pp. 471, with 166 illustrations, including 4 in color. St. Louis: Mosby, 1966.

Heritable Disorders of Connective Tissue, 3rd ed. Victor A. McKusick, M.D. Price, $18.50. Pp. 499, with 190 illustrations and 2 in color. St. Louis: Mosby, 1966.

New Drugs, 1966 Edition. Evaluated by the A.M.A. Council on Drugs. Price (paper), $4.00. Pp. 592. Chicago: American Medical Association, 1966.

CIBA Foundation Symposium: Transcultural Psychiatry. Edited by A. V. S. deReuck, M.Sc., D.I.C., A.R.C.S., and Ruth Porter, M.R.C.P. Price, $12.00. Pp. 396, with 10 illustrations. Boston: Little, 1965.

Blood Diseases of Infancy and Childhood, 2nd ed. Carl H. Smith, M.A., M.D. Price, $22.00. Pp. 800, with 85 illustrations and 1 in color. St. Louis: Mosby, 1966.

Symposium on Surgery of the Ocular Adnexa. Transactions of the New Orleans Academy of Ophthalmology. Contributors: Arthur Gerard DeVoe, M.D., Sidney A. Fox, M.D., Howard Naquin, M.D., T. E. Sanders, M.D., Byron Smith, M.D., Everett R. Veirs, M.D., and Joseph A. C. Wadsworth, M.D. Price, $16.00. Pp. 245, illustrated. St. Louis: Mosby, 1966.

United States Army in World War II: The Technical Services. The Medical Department: Medical Service in the Mediterranean and Minor Theaters. Charles M. Wiltse, Ph.D., Litt.D. Price, $5.00. Pp. 664, with 39 tables, 43 maps, and 128 illustrations. Washington, D. C.: Superintendent of Documents, U. S. Government Printing Office, 1965.

CIBA Foundation Symposium: Preimplantation Stages of Pregnancy. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I.Biol., and B. A. O'Connor. Price, $13.50. Pp. 430, with 153 illustrations. Boston: Little, 1965.

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Contraindications: In hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions.

Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised; especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of pre-existing symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dose—operation of motor vehicles, machinery or other activity requiring alertness should be avoided. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia, the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor, and respiratory collapse.

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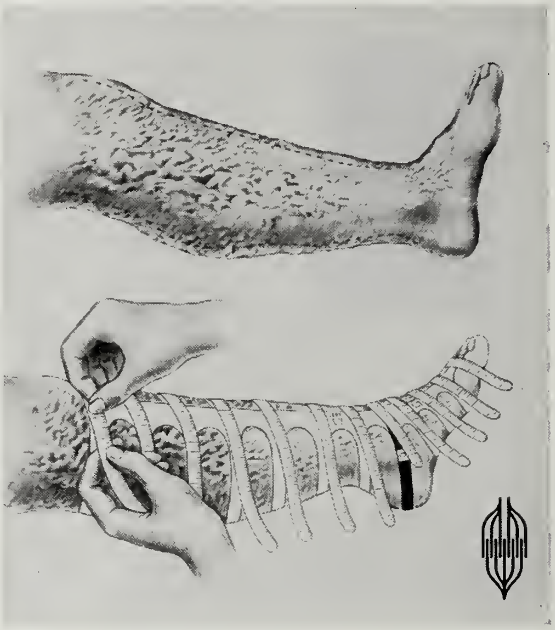

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September 9: Medical and Chirurgical Faculty of the State of Maryland. Ocean City, Md. Address: Mr. John Sargeant, *Executive Secretary*, 1211 Cathedral Street, Baltimore, Md. 21201.

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September 16–24: American Society of Clinical Pathologists. Washington Hilton Hotel, Washington. Address: Miss Martha Damron, Administrative Secretary, 445 North Lake Shore Drive, Chicago, Ill. 60611.

September 17–23: College of American Pathologists. Washington Hilton Hotel, Washington. Address: Mr. Oliver J. Neibel, Jr., Administrative Secretary, 230 North Michigan Avenue, Chicago, Ill. 60601.

September 25–30: III International Congress of Nephrology. Washington Hilton Hotel, Washington. Address: Secretariat, III International Congress of Nephrology, 9650 Wisconsin Avenue, Washington, D. C. 20014.

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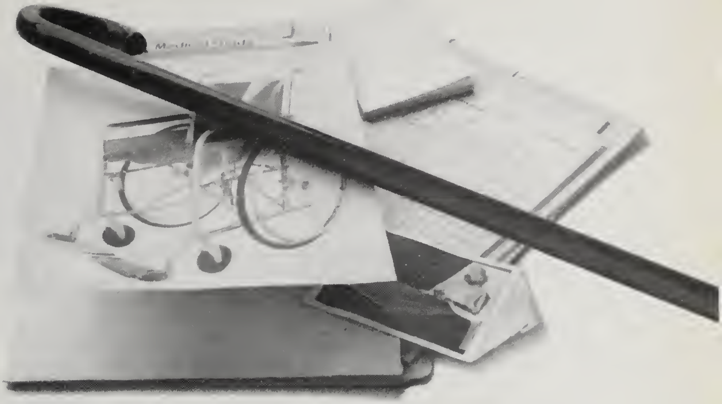

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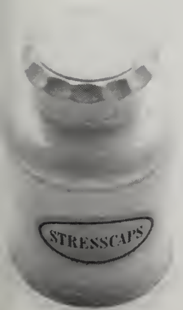

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MEDICAL ANNALS

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Myocarditis: A Review of the Development of the Concept*

WILLIAM C. MANION, M.D.†

The seriousness of an inflammatory involvement of the myocardium and the difficulties inherent in making the diagnosis have long been appreciated. James Johnson,[1] in his treatise published in 1826, stated that " 'Carditis' is one of the most dangerous diseases to which the human frame is liable." He pointed out that if the practitioner requires full development of all the symptoms before making the diagnosis of "carditis," as indicated by Cullen in his definition of "carditis,"‡ then he may "be lulled into fatal security." So, even 31 years before the publication of Virchow's "Cellular Pathology," the gravity of an inflammatory involvement of the myocardium was recognized and appreciated as was the occasional paucity of the clinical symptoms it might produce.

Historically, the development or, perhaps better, the evolution of the concept of myocarditis may be divided into 4 periods, a division made possible by periodic advancements in scientific knowledge and technical developments which both altered and influenced the interpretation and concept of the problem. The development of Virchow's theory of cellular pathology and the more extensive use of microscopic anatomy, the germ theory of disease, the beginning of the science of bacteriology and the introduction of bacteriologic methods of investigation into the hospital laboratory, the development and routine use of the electrocardiogram and the X-ray, and the discovery of viruses and the development of viral recovery techniques have all played a role, some advantageously, some less favorably, in the development of our present concept of the problem.

Prior to 1860 the morbid anatomists of the early period were concerned chiefly with the gross findings in the heart. The case reports of this period dealt mostly with those changes evident to the naked eye, i.e., hypertrophy, dilatation, fibrosis, calcification, and abscesses. Microscopic examinations were rarely done, and bacteriologic cultures were as yet unknown. The importance of vascular lesions and their possible effects on the myocardium were not recognized, and consequently it is difficult to evaluate the case reports of myocarditis during this period, since it appears that the term was applied to all the afflictions of the myocardium regardless of whether they were inflammatory, vascular, or degenerative in origin. Therefore, the case reports of this period must be accepted in the light of the knowledge and techniques available to the investigators of the period.

In addition to directing attention to the possible inflammatory involvement of the heart muscle the most important contribution of this period was the introduction of the term "myocarditis" into the medical nomenclature. The term apparently was first used by Sobernheim[2] in 1837 in his book, *"Praktische Diagnostik der innern Krankheiten,"* to describe an inflammation of the heart muscle, *"Entzundung der Muskelsubstanz des Herzens-Myokarditis."* However, from his description of the autopsy findings to be anticipated in such cases it is apparent that most of his observations were macroscopic and that he apparently included some conditions which would probably be excluded from the present interpretation of the term. While Sobernheim must be credited with the introduction of the term "myocarditis," he was not the first author on this subject, and in his text he refers to several others, among them Senac, Metzger, Von Eyerl, Frank, Corvisart, Testa, Laennec, and Krause. In the English literature the publications of Stanley[3, 4] and Salter[5] are noteworthy.

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‡ "Carditis" was defined by Cullen as "Pyrexia, dolor in regione cordis; anxietas, spiritus difficeles; tussis; pulsus inequalus; palpitio; syncope."

Stanley's case is that of a 12-year-old boy who died with what was considered clinically to be brain disease, but at postmortem examination was found to be an acute inflammation of the heart muscle "without pus." Salter's case was that of a 50-year-old man with a history of sudden onset of chest pain while walking, first of short duration but recurring 6 weeks later, accompanied by diffuse perspiration and syncope, with extension of the pain to the left arm. The gross findings were interpreted as chronic inflammation of the heart muscle; however, in light of our present knowledge the clinical history would seem more compatible with an acute myocardial infarction. This case typifies the deficiencies in the reports of this period, which consist chiefly of good gross descriptions while lacking in other essential information that would allow proper classification of the cases.

Considering, however, that the significance of the effects of vascular disease on the myocardium was still not recognized and that the knowledge of infectious disease was limited, the reports of this period must be accepted chiefly for their historical value. We must acknowledge, however, some of the clinical and gross observations of this period which were extremely good and were not only confirmed by later observations but also served to direct attention to the heart lesions, particularly in the case of diphtheria.[6, 7, 8]

The second period in the development of the concept of myocarditis began about 1860 when the influence of Virchow's theory of cellular pathology (1857) accelerated and when gross and microscopic anatomy began to broaden and mature. Bacteriology was in its infancy at the beginning of this period, and the germ theory of disease was beginning to become fact. The entire period was directly influenced by the work of Pasteur, Koch, and other workers in the isolation and identification of the causative organisms of disease. Because of the tremendous developments in the field of bacteriology, it was quite natural that interest should develop in the pathology of infectious diseases, and since cardiac symptoms and sudden death are not an infrequent happening in infectious disease, particularly in typhoid fever and diphtheria, it was also natural that attention should be directed toward the heart.

In 1867, Bernheim,[9] in his thesis on acute myocarditis, recognized both an acute and chronic form of myocarditis and noted the predilection for the left ventricle of the heart. As for the etiology, however, he admitted it was obscure, but he considered chills, trauma, pericarditis, endocarditis, rheumatism, syphilis, alcoholism, and vascular obstruction as possibilities. Two years later, Hayem[10] described the presence of interstitial myocarditis in a patient dying of typhoid fever. This was soon followed by reports of myocardial involvement in diphtheria,[11-21] scarlet fever,[10, 17, 22, 23] smallpox,[10, 24] erysipelas,[10] gonorrhea,[15] and tuberculosis. Diphtheria was extensively studied during this period,[6, 7, 8, 10, 14, 15, 18, 25-29] and from these studies arose many of the controversies and problems that were to cloud the concept of myocarditis for many years to come; in fact, some of the controversies generated in this period are still major problems today. For this reason, a brief review of these reports is probably worthwhile.

The anatomic changes in the heart muscle in diphtheria were first described by Rosenbach,[18] Leyden,[15] and Huguenin,[14] although other authors including Bristowe,[6] Ranvier,[8] and Hillier,[7] on the basis of their clinical and macroscopic observations, had already pointed to the degeneration of the heart muscle fibers as the cause of the serious, well-known clinical heart symptoms. These authors maintained that the macroscopic parenchymatous changes in the myocardium were responsible for the heart "paralysis" occurring with diphtheria.

While a good correlation appeared to exist between the clinical symptoms and the gross observations at this time, it soon became apparent that there were marked variations in the reported microscopic findings in the myocardium. Many authors reported only a parenchymatous change, while others found an interstitial myocardial change, or even on occasion a combination of the 2 forms of lesions. The morphologic changes in the heart were variously interpreted. Hayem[10] and Martin[27] considered the primary lesion of the heart as an inflammation of the intima of the blood vessels with extension to the media, adventitia, and the adjacent connective tissue, with a resultant scar in the heart muscle. Mosler,[28] in his study of the hearts of 2 children who died of diphtheria, found only a fatty degeneration of the musculature. Bouchut[25] and Labadie-Lagrove[26] stated that their findings were chiefly those of fatty degeneration of the heart muscle and that only rarely did waxy or granular degeneration of the muscle fibers occur. Rosenbach,[18] in his series of well studied cases, found an extensive fatty, granular and waxy degeneration of the myocardial fibers, which was most severe in the immediate subendocardial myocardium and around the origin of the great vessels, and which gradually diminished as the middle of the myocardium was approached.

Some entirely different findings were reported by Leyden[15] from his microscopic study of 3 cases of diphtheria, 1 of which was a sudden death case. He found a slight fatty degeneration with diffuse irregular round-cell infiltration of the interstitial and perivascular tissue, as well as the presence of scattered older myocardial lesions. He believed that the presence of the myocarditis was responsible for paralysis of the heart and was the cause of death. Guttman,[30] on the other hand, found only cloudy swelling in the hearts of those dying of infectious diseases, including diphtheria, and never saw any inflammatory foci. Oertel[16] reported the presence of foci of extravasated blood, as well as foci of interstitial cellular infiltration in cases of severe diphtheria, and he further noted that when the disease lasted for a long time, or when it was severe, or when the patient died suddenly, the muscle fibers also showed an advanced fatty degeneration. Gombault,[31] on the other hand, found a normal myocardium in the 1 case that he studied.

In view of the marked variation of the microscopic findings, it is no wonder that confusion existed concerning the heart changes in diphtheria. Later publications, however, particularly that of Hallwach[13] in which 14 cases were studied, served to bring some order to the dilemma and demonstrated that both parenchymatous and interstitial lesions could be found in the hearts of fatal cases; they pointed out, too, that the time interval between onset and demise, as well as the severity of the infection, were important factors in determining the morphology of the heart lesion.

Viewed retrospectively, in the light of our present knowledge diphtheria proved to be the ideal disease for perplexing the investigators; true, it is an infectious disease, and its etiologic agent, the *Corynebacterium diphtheriae*, could be cultured from the throat and identified. The clinical symptoms it presented frequently indicated heart involvement and heart failure, and sudden unexpected death was not uncommon. The hearts in many of these cases showed gross changes indicative of heart involvement, but the microscopic findings were variously reported as those of parenchymatous myocarditis, fatty degeneration, interstitial myocarditis, or myocardial fibrosis; often they revealed no changes at all. To further confuse the investigators, in contrast to other infectious diseases, the myocardial changes were not the direct result of the infectious agent but were caused by the toxins produced. We also now recognize that the myocardial changes vary with the development of the disease and hence can range from simple tinctorial changes in the stained section to interstitial cellular infiltration, fatty degeneration, or even well-developed scars. Since the duration and the severity of the infection varied with each case, the microscopic findings were accordingly variable, and consequently different descriptive terms were applied to these changes, such as cloudy swelling, fatty degeneration, interstitial myocarditis, or myocardial fibrosis. Only when comparable cases with similar survival periods were compared was it proven that these changes were not necessarily different manifestations of the disease but were actually representative of different phases in the broad spectrum of changes associated with the duration of the disease. From these differences in morphologic findings and interpretations, however, were to arise many of the problems in distinguishing myocarditis, particularly the artificial distinction between interstitial and parenchymatous inflammation that is still being discussed in our time.

Since much of this period was concerned with myocarditis in infectious diseases it was natural that soon the problem of chronic myocarditis should arise. Ruhle,[32] writing in the *Deutsches Archiv für klinische Medicin* in 1878 on the diagnosis of myocarditis, recognized both an acute and chronic form of myocarditis, each having a circumscribed and diffuse type. The acute circumscribed form of myocarditis was evidenced by localized abscesses of the heart, and clinically the patients showed signs of heart weakness, periods of unconsciousness, anxiety and, terminally, heart paralysis. Ruhle noted that the acute diffuse type of myocarditis which he described as very rare could be secondary to a pyemia or could occur as a primary rheumatic disease. He credited the previous description of this form of myocarditis to Rindfleisch[33] whose case was that of a 35-year-old worker with a history of chest injury who developed signs of heart weakness with rapid pulse and dilatation of the heart. At autopsy numerous needle-head-sized abscesses were found in the heart from which staphylococci were recovered.

In addition to the description of the acute diffuse type Ruhle also mentioned a "primary acute diffuse type," which he stated was usually unrecognized until the death of the patient. It was his belief that the acute diffuse type of myocarditis could last for a long time and that it might culminate in a chronic form of myocarditis. He reported 8 cases of the chronic form, which were characterized by scarring of the myocardium, either circumscribed or diffuse in nature. He noted the poor prognosis, its occurrence chiefly in the left ventricle, and the possible relationship to syphilis. From this group of cases Ruhle excluded all cases with heart anomalies, valve lesions, pericarditis, and cases of fatty degeneration. However, since he noted the association of the lesion with the site of aneurysm formation, it may be that some of his cases were myocardial infarctions.

With interest during this period focused on the heart and its changes in infectious diseases, and with the increase in microscopic investigation of the heart, attention was soon directed toward the occurrence of myocarditis in the absence of this relationship. Reference has already been made to Ruhle's "primary acute diffuse myocarditis"[32] which he stated was usually not recognized until the death of the patient. Cases of this type were previously described by Steffen,[34] Rindfleisch,[33] Wolf,[35] Freund,[36] and Ruhle.[32] It was Fiedler,[37] though, in 1899 who drew attention to "primary acute diffuse myocarditis" when he presented 4 cases with microscopic findings of an acute interstitial myocarditis, similar to the findings described by Hayem[10] and Romberg[17] in their cases of diphtheria, typhoid fever and scarlet fever. However, in Fiedler's cases,[37] there were no clinical symptoms suggesting these diseases, nor were there changes in any other organs. These cases were described as having "an acute, almost sudden onset of myocarditis, with chills and which are highly probably caused by microörganisms. As a rule, it is usually in young people and occurs without or with only slight fever. The pulse is almost always weak, greatly increased, very rarely slow. The heart is dilated to the right and to the left. Heart action is irregular. Dyspnea, cyanosis, and signs of stasis in both the peripheral and pulmonary circulation are present, and there is much proneness to heart weakness. The spleen as a rule is not enlarged. The chief findings are an elevated albuminuria and signs of circulatory stasis in the kidney. The sensorium is intact. At times in the course of the disease, or toward the end, there are attacks of headaches. The disease is localized chiefly in the myocardium and presents there as an interstitial myocarditis, while the other organs remain free or only show secondary changes in the course of the disease. It consists truly as an infection of its own. This disease has in common with other infectious diseases, such as scarlet fever, diphtheria, and typhoid fever, similar pathologic changes in the heart muscle but does not have anything in common with rheumatism, syphilis, arteriosclerosis, or the usual form of sepsis or septicopyemias. The prognosis is generally fatal, and as a rule the disease ends fatally in from 5 to 17 days. Recovery is not excluded, but whether complete recovery can be achieved seems as yet doubtful." *

Other papers on acute isolated interstitial myocarditis soon followed. We should note particularly the publications of Josserand and Gallavardin[38] and Sellentin.[23] The first authors noted the occurrence of the myocarditis in the absence of an antecedent disease and designated it as "primitive" or primary in the heart. The latter author, who published his report in 1904, noted that awareness of this form of myocarditis had only developed in the previous 10 years, and he drew attention to the case reports of Fiedler,[37] Rindfleisch,[33] Freund,[36] and Ruhle.[32] He defined his use of the term "isolated" as "without accompanying septic signs in other organs." It is of interest, however, to note that of the 2 cases he reported 1 occurred in a 16-year-old boy who had had a carbuncle incised on his lower jaw just 3 weeks before the onset of clinical symptoms, while the other occurred in a 24-year-old woman who 6 weeks postpartum developed a sudden onset of pain in the right lower side, and whose death rapidly followed a bimanual examination of the uterus. Whether these 2 cases actually fit this designation is open to question.

In the English literature Carpenter's report[39] in 1903 on uncomplicated myocarditis in children is most interesting. In it he recognized

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* Translation by author (W.C.M.) of Baensch's abstract of Fiedler.[37]

both a parenchymatous and interstitial form of myocarditis with both a circumscribed and diffuse type of each. He was also aware of the albuminous fatty and waxy changes that might occur in the heart as a result of toxins, and that were, he thought, almost impossible to diagnose clinically. He recognized both an acute and chronic form of interstitial myocarditis and noted as a common cause the pyemias resulting from bone and joint trouble. He drew attention to Fisher's report of small fibroid patches which he frequently found scattered throughout the heart in deaths from mitral stenosis. Carpenter also noted that sclerotic patches in the heart might have their origin in occlusion of the coronary arteries, syphilitic or otherwise. Thus, we begin to see here doubts as to the origin of the scars of the myocardium which Ruhle had previously accepted as indicative of a chronic myocarditis; and simultaneously we have the beginning awareness of the importance of vascular disease in the production of myocardial scars, a recognition that was to characterize much of the third phase in the historical development of the concept of myocarditis.

The third period of development was ushered in by 4 major contributions that greatly influenced not only the problem of myocarditis but of all heart disease. They were the discovery of the X-ray by Roentgen in 1895, the introduction of the electrocardiograph by Einthoven in 1906, the recognition of the specific lesion of rheumatic heart disease by Aschoff[40] in 1905, and the recognition and establishment of coronary thrombosis as a clinical entity by Herrick[41] in 1912. (To these we might add the development of the clinical Wassermann test for syphilis, and the report of Anitschkow[42] on the histogenesis of myocardial changes with intoxication, because they, too, influenced the development of the concept of myocarditis.) Although the discovery of the X-ray by Roentgen was earlier, the third phase can roughly be said to commence about 1910, since it was some time before the X-ray and the electrocardiogram became clinical tools.

Aided by these 2 methods of investigation, the clinician was better able to study a patient, and soon he began to detect minimal clinical involvement of the heart which previously would have passed unnoticed. With the use of these new tools it soon became evident that the heart was frequently involved during the course of many systemic diseases.

Aschoff's publication,[40] though not the first concerning the lesions in the heart in rheumatic fever, drew attention to the myocardial lesions and brought recognition to a specific lesion, the Aschoff nodule of active rheumatic heart disease. Stimulated by his work, many investigations were undertaken, and soon rheumatic heart disease was recognized as one of the leading causes of myocarditis. Herrick's publication greatly influenced clinical medicine and opinion, and, together with the wider use of the electrocardiogram, heralded the beginning of the separation of the myocardial changes resulting from vascular disease from those of true myocarditis. Complete acceptance of the distinction, however, was not immediate, and even after coronary thrombosis had become an accepted clinical entity, the term "myocarditis" was frequently applied to the myocardial changes associated with coronary thrombosis.

Interest in the occurrence of myocarditis in infectious diseases was further increased with the onset of World War I, especially interest in those diseases which accompany war and poor sanitary conditions. In 1909, while studying the so-called Rocky Mountain spotted fever in the United States, Ricketts[43] discovered in the blood of patients and in tick vectors the causative agents of the disease in the forms of extremely small, distinctive formations, which he called "diplococcoid" bodies, later given the name *Rickettsia rickettsii*. In 1913 the celebrated Czech scientist Prowazek, working with Hegler on typhus fever in Siberia, also discovered similar formations in lice fed on typhus fever patients.[44] Similar discoveries in typhus-infected lice were published in 1914 by Sergent, Foley, and Vialatte[45] working in Algeria. Finally, Prowazek and Rocha Lima, undertaking a joint investigation of typhus-infected lice, confirmed the presence of formations similar to those discovered earlier by Prowazek in Siberia. Continuing his investigations after Prowazek's death from typhus, Rocha Lima was able to report with exhaustive proof the detection and isolation of the agent of typhus fever in lice infected by feeding on infected patients. With interest stimulated by these discoveries, investigations continued on this interesting group of diseases, and soon reports of myocarditis occurring in the course of these diseases began to appear.[46-49]

While World War I raged, worldwide epidemics of influenza broke out. As Saphir[50] has pointed out concerning the reports of these epidemics, it is difficult to ascertain the exact meaning of the term "influenza," or its synonyms, "grippe infections" or "flu," as used in these reports, and it is uncertain whether the cases reported were caused by the Pfeiffer's bacillus, the hemolytic streptococcus, or a virus, since the knowledge concerning these diseases had not yet developed. Whatever the etiologies of these cases were, myocarditis was occasionally reported as occurring with them. The occurrence of myocarditis in influenza was first reported by Schmorl,[51] although about the same time Lucke et al[52] reported that the heart was practically always affected in fatal cases; however, they described only parenchymatous changes with vacuolization of the fibers. The findings of the latter authors contrasted with the rarity of its occurrence, as reported later by Wolbach and Frothingham[53] in their study of 27 fatal cases occurring at Camp Devens in 1918; at that time they stated that the heart muscle appeared to escape injury during the course of the disease.

Interest in the acute interstitial or isolated myocarditis also continued during this period; Scott and Saphir[54] were able to collect 30 cases reported in the literature up to 1924. Although varying opinions as to etiology, such as infectious or toxic, were suggested in these publications, most of the supportive evidence was unconvincing.

While there were many developments during and shortly following the cessation of World War I that expanded the spectrum of diseases in which myocarditis could occur, it soon became apparent that complete harmony did not exist with regard to the meaning and application of the term. The reason for this divergence of opinion is difficult to pinpoint, but it may be, as Saphir has pointed out, that the term fell into disrepute because of its continued indiscriminate use, particularly on death certificates, without any supportive morphologic evidence. Furthermore, it appears that the term "chronic myocarditis" was frequently applied to any lesion in the heart, regardless of whether the lesion was primarily vascular, degenerative, or inflammatory in character. Certainly with the term being used in this meaningless sense, the reluctance of city and state health departments to accept "chronic myocarditis" as a cause of death, as reported by Saphir, seems justifiable.

Among the other factors which may have played a role in arousing this state of disrepute were, first, the initial attempts to classify diseases of the heart on the basis of etiology, structural change, and functional state; second, the low degree of accuracy in clinical diagnosis; and third, the lack of available technical facilities and techniques for demonstrating etiologic agents and morphologic changes. As early as 1914 we find some disillusionment with the meaning of the term when Cabot[55] stated that "the microörganisms of rheumatism and of syphilis, the ravages of arterial disease, and perhaps many other causes may produce the lesions of chronic fibrous myocarditis, with or without recognizable symptoms. A diagnosis of myocarditis is like a diagnosis of 'ulcer'; it calls for an etiologic qualification, such as syphilitic or tuberculosis." In 1921 White and Myers[56] in their classification of cardiac diagnosis stated, "The old-fashioned terms, such as mitral regurgitation and myocarditis, and cardiac dilatation, any of which often suffered in the past to cover the entire diagnosis of a case of heart disease, are rapidly being discarded in the sense in which they were formerly used, and yet even now in medical centers, as well as in distant rural communities, such diagnoses are sometimes made and apparently satisfied." Twelve years later, Sir Thomas Lewis[57] in his textbook, "Diseases of the Heart," wrote, "The only form of inflammation of the heart muscle that is all common is rheumatic in origin and it takes an acute or more often subacute form. Occasionally, inflammation occurs in other states and fatal infections, diffusely in diphtheria, locally in pyemia. The term myocarditis has often been allowed most loosely to comprise all the altered states of the muscle, real or supposed. It has been employed improperly as an equivalent of myocardial weakness. Actually, the use of the term 'myocarditis' is scarcely to be justified clinically, except in relation to rheumatism, and here the term 'carditis' is sounder. The description of myocarditis, acute or chronic, as a separate disease with its special symptoms and signs needlessly complicates a general description of cardiac disease."

Therefore, from the opinions thus expressed, it can be seen that there existed a marked variation in the meaning and significance of the term "myocarditis" as used by different authors, some of whom applied it to the myocardial changes in a large number of diseases, while others restricted its meaning only to the changes found in the myocardium in rheumatic fever and possibly diphtheria. Attempts to restore some meaning and significance to the term were soon appearing; Clawson[58] in 1928 used the term "myocarditis" in his paper on the subject, "only where an inflammatory process in the heart muscle is made evident by an exudative or proliferative cellular reaction." He stated, however, on the basis of his study of 429 cases of cardiac failure, that "It is doubtful whether the clinical diagnosis of either acute or chronic myocarditis should be made, even though such a condition commonly exists in association with a valvulitis. It is certain that what is called 'chronic myocarditis' clinically is chronic heart failure without valvular injury, is not an inflammatory condition, and in most cases is not any other condition in the myocardium showing an anatomical basis for the failure." Riesman[59] in 1926 introduced the term "myocardosis" in an effort to account for the fibrotic noninflammatory changes in the heart in cases of chronic heart disease. Despite these attempts to secure a proper clinical place for the term "myocarditis" there still remained much uncertainty as to its meaning because of its prior history. If the term "myocarditis" appeared restricted, the term "chronic myocarditis" had even less significance; thus, in 1933 in his paper on "The Pathology of Chronic Myocarditis" Warren[60] qualified his introduction to the subject as follows: "To talk on the pathology of chronic myocarditis is particularly difficult, inasmuch as in many cases the anatomic changes in the heart are negligible in importance or indeed at times almost completely absent. Chronic myocarditis is a clinical, rather than a pathologic term." In the same issue of the journal, Christian,[61] in an article entitled "The Diagnosis of Chronic Nonvalvular Cardiac Disease (Chronic Myocarditis)," wrote, "Terminology is unsatisfactory. Chronic nonvalvular cardiac diseases, if one understands that the pericardium is not concerned, is satisfactorily descriptive. Chronic myocarditis carries the idea of inflammation with connective tissue proliferation, and this usually is lacking. However, in classical Greek, the term '*itis*' did not mean inflammation of, but merely 'concerning,' or 'about,' and in this classical sense, chronic myocarditis is a justified title." The prevailing opinion in existence at the end of this period is well expressed by White,[62] in the 1937 edition of his textbook: "The clinical diagnosis of myocarditis so freely used in the past has wrongly included many other conditions, in particular the frequent instances of hypertensive heart disease in which there is cardiac hypertrophy and enlargement but no inflammatory reaction in the muscle; the term 'myocarditis' has also wrongly included frequent instances of coronary disease, in which degenerative changes, fibrosis and atrophy may occur without actual inflammatory process. In the attempt to diagnose heart disease more accurately, the term 'myocarditis' is being wisely abandoned in large part; we must remember, nevertheless, that there does exist such a condition as myocarditis."

The fourth period of development in the concept of myocarditis arbitrarily began with the onset of World War II, roughly in 1940. The opportunity afforded by World War II to study large numbers of patients afflicted with diseases of many different etiologies did much to bring myocarditis into its true focus. Here for the first time large-scale clinical investigative studies on the afflicted patients were possible with routine use of the electrocardiogram, the chest X-ray film, and other diagnostic aids. In many of these diseases indications of myocardial involvement were detected clinically, and, fortunately, in many of the fatal cases, postmortem studies, including bacteriologic and microscopic examinations of the hearts, were possible. The careful morphologic studies of Gore and Saphir[63, 64, 65] based on this material revealed that myocarditis was a frequent complication of many diseases and served to again establish the wide scope of diseases in which myocarditis could occur.

Another most important development early in this period was the substantiation of viral infections of the heart. While virus myocarditis had been suspected prior to this period, actual recovery of the virus from the heart was not technically possible. Although virology had its beginning in 1892 when Iwanowski[66] discovered that the juices of plants infected with tobacco mosaic remained infectious after passing through fine filters, its overall development was slow until 1930. The sudden and rapid development during the following decade was due in great part to 3 technical discoveries made during this period.[67] They were the discovery by Woodruff and Goodpasture of a method to cultivate viruses on the chick embryo, the invention of the ultra centrifuge, its application to virology, and the creation of the electron microscope. With these developments the possibility of viral recovery from infected individuals and tissues became a reality.[68] The first apparent successful recovery of the virus from a case in which myocarditis occurred appears to be that of Finland et al[69] who reported 2 fatal cases of influenza, both in adults (1 in a male, and 1 in a female), in which a severe diffuse myocarditis was found and influenza virus A was recovered from the lungs. Since then other reports of successful viral recoveries have been reported by other authors, including van Creveld and deJager[70] (Coxsackie B virus), Montgomery et al[71] (Coxsackie B virus), Javett et al[72] (Coxsackie B virus), Kibrick and Benirschke[73] (Coxsackie B4 virus), Hosier and Newton[74] (Coxsackie B4 virus), and Delaney and Fukuaga[75] (Coxsackie B4).

Another development of this period was the introduction, first, of reliable gravimetric methods, and later of spectrophotometric methods for the determination of electrolytes in the clinical laboratory. Aided by these methods and instruments, reliable and quick determination of sodium, potassium and calcium levels became a reality in clinical investigation, and soon we began to see the reports of the effects of electrolyte disturbances on the heart. The earliest observation appears to be that of Schrader et al[76] who noted the occurrence of multiple foci of myocarditis and necrosis in the hearts of rats kept on a potassium-deficient diet. This was followed by the reports of Thomas, Mylon and Winternitz[77] and Follis, Orent-Keiles and McCollum[78] describing similar changes in the hearts of rats on low potassium diets. Cannon and his co-workers[79] in later publications showed that the effects of potassium deficiency in protein-depleted rats could be profoundly affected by the administration of excess sodium chloride either in the diet or parenterally. Selye[80] has further expanded many aspects of this intriguing problem in a book published in 1958.

Space does not allow for complete coverage of all the developments in medicine that have influenced the problem of myocarditis, and only those contributions that seemed most significant have been touched upon. Other, probably equally significant contributions may have been neglected, perhaps completely overlooked, but this is unintentional. We realize that to fully appreciate the problem of myocarditis one must be aware of all the developments that have influenced its evolution.

To say that there is now complete agreement as to the meaning of the term "myocarditis" is not yet possible. At the present time there is not even complete accord as to what myocardial changes constitute a myocarditis, nor is the parenchymatous lesion of the heart recognized as a true inflammation by everyone. In view of this it is necessary that we carefully define the term "myocarditis" and strictly adhere to its definition, otherwise the term will soon revert to its former status and again become meaningless. If we accept the original meaning as intended by Sobernheim, who defined myocarditis as "an inflammation of the heart muscle," and from this omit those lesions resulting from overt ischemia, we shall have a term that has meaning. Should we use the term "inflammation" in its broad sense, or should we, as Clawson did, restrict it to "only where an inflammatory process in the heart muscle is made evident by an exudative or proliferative cellular reaction"?

If we agree to the latter designation we necessarily restrict our diagnosis to a phase in the spectrum of the inflammatory change. It is true that by doing so the term is given some meaning, though in a restrictive sense; however, it is less prone to become a "wastebasket" term. As yet this is perhaps the best designation for the term, since we can all agree on the presence or absence of inflammatory cells in the myocardium. It is my desire, however, that the term might come to include the whole spectrum of an inflammatory response in the heart, including the early parenchymatous change, the cellular infiltration stage, and the terminal scar. It is realized, however, that the fulfillment of this expectation must wait, since techniques are not yet available that reveal the etiologic nature of a scar or identify the early parenchymatous changes with any certainty. It is anticipated that future application of histochemical techniques might make this goal possible. Perhaps enzymatic or fluorescent techniques can be developed that will identify the early parenchymatous injury or give insight into the origin of some of the terminal scars. Until this is achieved, however, we must take care to prevent indiscriminate use of the term.

Today, despite the tremendous progress made in medicine, many problems still exist regarding myocarditis. To enumerate a few, there is still the question of isolated or idiopathic myocarditis; as yet the relationship of myocarditis to idiopathic hypertrophy is not clear; and there still remains the problem of allergic or hypersensitivity myocarditis. The association of electrolyte imbalance and myocarditis and myocardial necrosis needs further study. All of these are major issues and all will require close teamwork on the part of the clinician, the pathologist, the virologist, and the biochemist. To this end let us hope that future generations will point to ours as a productive generation that made a positive contribution to the problem of myocarditis.

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Medical Education and the Community*

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I AM HONORED and pleased to have been nominated for the Kober Lectureship in this first year of my tenure as Surgeon General of the Public Health Service.

Dr. George M. Kober, who established this lectureship in 1923 on the fiftieth anniversary of his graduation from this medical school, was evidently a man whose vision spanned the entire health world. His commitment to scientific medicine marked him as being well ahead of his time; in fact, I am informed that the immediate object of the first lecture was to present scientific data to support research at a time of vigorous antivivisectionist activity in Congressional hearings—a subject as timely as tomorrow's newspaper. At the same time he had an abiding interest in preventive medicine as well as in medical care.

More than 4 decades have passed since the first Kober Lecture was presented here. They have been the most turbulent decades in human history. In the world of medicine these 4 decades have witnessed a greater accumulation of knowledge than in any previous 4 centuries, perhaps than in all the previous annals of medicine.

Yet the basic elements of the medical equation remain essentially the same. Our thirst for new knowledge is as great as ever, and our investment in acquiring that knowledge through research has multiplied manifold. Our need to apply the benefits of new knowledge through preventive medicine and medical care becomes more urgent with every passing year. And the medical school remains the pivotal institution, both in generating new knowledge and in shaping the course of our medical future by the training it gives to oncoming generations of physicians.

What kind of medical future are we shaping? Are we preparing the new generations of physicians to serve the health needs of the next decade and the next century?

There is a lot of talk these days about the "crisis" in American medicine. Granting that the word "crisis" has been badly stretched out of shape by overuse, I think we are at a point of crisis in something like its original medical sense of "a turning-point." I believe we have reached a crisis of unfulfilled expectation on the part of the people we serve.

The American people have accepted the principle that the best in health care should be theirs by birthright. In part we have brought this acceptance upon ourselves by proclaiming the wonders of scientific medicine. In part it has evolved out of great economic and social changes in the society as a whole. In any event, the people have set a new goal for us: the best in medical care, not for some of the people some of the time, but for all of the people all of the time. The great legislative programs in health of the past few years are an expression, by the President and the Congress, of this aspiration.

It is up to us to raise our sights so as to hit the new target. And I believe that the medical education establishment which most of you represent, as both students and teachers, is the institution in our society that must take the lead. That is why I have titled this lecture, "Medical Education and the Community."

Let us take a closer look at this present crisis of ours. And in doing so let us try to step outside our professional personality and look at medicine through the eyes of the people we serve, the people whose aspirations will be the true measure of our success.

As a profession we tend to talk a great deal about the physician-patient relationship, frequently vowing to defend it to the death, but we give very little thought to the patient-physician relationship, viewed from the other side.

Occasionally a brave patient speaks out. Alistair Cooke recently observed that the patient-physician relationship is one of constant humiliation for the patient. When he sees the doctor all of his defenses are down, literally and figuratively. He is both worried and undressed, while the physician is both serene and fully clad. He desperately wants to know what is going on inside himself, and yet he is reasonably sure that the doctor will not tell him anything.

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This kind of one-upmanship is not calculated to win friends. It is especially unlikely to do so when the patient has had to wait an hour for his brief and, to use Mr. Cooke's word, humiliating session, and when the patient and doctor are almost total strangers to each other.

Does it matter? Do we need to win friends?

I think it matters a great deal. It is easy enough for us to turn a deaf ear to the mounting chorus of public grumbles. We can justify our loss of touch with the individual patient on the basis of efficiency. We can justify our extreme specialization on the basis of science. But when we are through justifying ourselves there is still something left out.

That "something" is the patient as a human being.

I recently came across a paper presented a couple of years ago at Stanford by William W. McPeak, Vice President of the Ford Foundation. The title, significantly, was "The Small, Frantic Voice of the Patient." Let me read you a paragraph from that paper:

"As the doctor becomes more the specialized scientist there necessarily follows a narrowing of the base for human contact. No one doubts that the shift in medicine has brought more gains than losses, but the gains do not permit us to ignore the losses, especially when the latter are so much in the patients' sphere. We must remember what medical care is all about and that the word 'care' has a human, as well as a technical, meaning."

In my judgment Mr. McPeak has hit the nail squarely on the head. American medicine stands in danger of losing the human meaning of the word "care." More and more, we meet people only on our own home grounds, in the warm, secure, efficient, antiseptic environment of the medical center. If we see them in their own setting of home and community at all, it is only in moments of absolute emergency. Both we and they are the losers. By lifting ourselves above the community where people live, we may render more efficient service but we do not give better care.

Let us not delude ourselves about the nature of community medicine. Compared with the familiar comfort of the insulated medical citadel, it is cold out there where people live. Sometimes it is downright unpleasant. But if our scientific wisdom is to have any relevance to human reality, we need to know what reality is like.

I returned a month ago from 2 weeks in South Viet Nam. This trip was, for me, a sobering experience. It was also a heartening one. I found it tragic but also exciting to see medical people working desperately hard against tremendous odds, trying to achieve what we take for granted.

If we can capture even a portion of that sense of urgency in American medicine we can find ways of delivering the best in modern medical care to all our people. This is the challenge to medical education. This is the heart of the crisis.

I have a fairly specific course of action in mind for American medical schools. First, however, since you have borne with me this long, let me back off a little bit and present briefly my interpretation of how we reached our present time of crisis.

This is not the first such moment of truth in the history of medical education. There have been at least 2 others since medicine emerged from its own Dark Ages. Each time, medical education has responded to the challenge of new conditions, first with the Flexner Report and its sequelae; second, with the swift development of medical specialization. We are now, I think, on the threshold of a third major departure.

The Flexner Report, more than half a century ago, fixed medical education and therefore medicine itself to the rising star of science. The developments that stemmed from this revolutionary document established the scientific base on which we have been building ever since. The Report set the stage for the swift advance of knowledge and the racing technology of medicine as we know it. It created the interlocking faculties, oriented toward the basic sciences, and the graduate school milieu that characterizes the university-medical school complex.

The second major response to crisis has been evolutionary rather than revolutionary. But it has been an evolution on an accelerating schedule. This is the development of specialization. It began to be visible as a significant trend in the 1920's and '30's. It has become the dominant theme of medical practice since World War II.

In a sense, of course, specialization was another outgrowth of the Flexner Report, because it is a necessary companion of scientific and technological advance. Medicine long ago outgrew the little black bag and the capacity for knowledge of the man carrying it. Medicine had to specialize or stagnate.

But specialization has inevitably led to several by-products whose implications have still not been deeply explored. It has led to residency training and the accompanying prolongation of medical education by from 2 to 7 years. As subspecializations develop within specialties, the temptation exists to lengthen it still more. Where, if anywhere, is the point of diminishing returns? Have we already passed it?

Specialization has completely altered the meaning of the physician-population ratio by which manpower needs have been measured for many years. We know that the gross ratio has remained fairly constant in recent years. We do not really know what the ratio means. The service provided by a given number of present-day physicians to a given number of consumers is vastly different from that which was provided 30 years ago. Some health needs are undoubtedly being met more successfully today, but I suspect that some are not being met as well.

Finally, specialization has created a medical school faculty which is itself oriented toward specialization. Most of your professors were nurtured in the specialized environment. They are completely at home only in the climate of the hospital complex which gives full rein to specialized practice. The system is self-generating, self-perpetuating, and self-accelerating.

This rapidly revolving system, complete in itself, has spun off many wonders. It has immeasurably heightened the potential of medicine.

But now we return to my point of departure. In harnessing itself to the upward spiral of science, medical education has lost, or threatens to lose, its linkage with people—with the health needs of individuals and families, perceived as they perceive them, in the homes and communities where they live.

We cannot afford this loss of touch. Therefore, my specific call to action for medical education is directed toward reëstablishing medicine's community roots.

I would urge the creation, in medical schools across the country, of a "third faculty" oriented toward the community. Dean Willard at Kentucky, who has pioneered in this field, calls it the "outside faculty" as contrasted with the conventional departments.

The task of this third faculty would be to prepare oncoming generations of students for practice in the community. It would conduct research on community grounds. It would experiment with new forms and patterns of service. And it would teach outside the institutional walls, using the community itself as its laboratory and classroom.

The existence of this third faculty would serve a double purpose. In addition to its educational function for the students it would also help to link existing community services with the medical centers. The third faculty would, in a sense, constitute a bridge between the 2 worlds of community and academic medicine. Its presence would encourage the flow of new knowledge into practice. This kind of linkage, I might add, is just as important right here in Washington as in the hinterlands—as important for suburban practice as for rural areas and urban slums.

Obviously, this new revolution—for it is nothing less—will not resolve the crisis overnight. Neither the Flexner Report nor the specialization movement produced instant miracles. But as it gains momentum it can, I believe, enable scientific and specialized medicine to fulfill its potential for all the people. Today's crisis is, as I have said, a crisis of unfulfilled public expectation. It is also a crisis of unfulfilled professional capability.

Let us examine some of the benefits that would evolve out of a conscious and deliberate effort to educate physicians for community service.

We have been talking for many years about the widening gap between the accumulation of scientific knowledge in biology and medicine and the widespread application of that knowledge for the benefit of people who need it. I am suggesting that that gap represents the distance between the family, with its health needs, and the medical center with its technology for health. What appears to be missing is a person, an institution, a procedure for bringing these together.

Traditionally that vanishing American, the family physician, has been assumed to play this role. But consider the young physician moving into practice this year. His entire education and experience have been in a university setting or a hospital. The great majority of his teachers and preceptors have had similarly limited experience within the walls of the citadel.

Can this young physician enter the community setting and serve the families of that community as their first line of contact, their initial port of call en route to the care they need? Some of them undoubtedly can, and will, but they will do it in a setting foreign to all their previous training and experience and contrary to much of the leadership to which they have been exposed. This is a formidable obstacle to place in the path of community medicine, where most medical practice actually takes place.

In short, as the physician specializes and subspecializes and as he is increasingly oriented to the hospital his ability to meet family health needs tends to diminish. The family, and often the individual within it, are treated on a piecemeal basis. The integral quality of the family and its community roots are threatened.

I am convinced, therefore, that the establishment of a link between family and hospital is a primary goal for the Nation's health enterprises in the years immediately ahead. Every person who is ill or injured should have a place to go for initial entrance into the health system. He should know where it is, how to obtain its services; and he should have confidence in it. Moreover, there must be established channels leading from these checkpoints into the course of treatment that will serve the individual best. Today the individual gets to the right place at the right time largely by happenstance. Many do not.

These entrance points into the health system do not now exist in a universally recognized form. The GP's office, the specialist's office, the public health clinic, the neighborhood health center, and the hospital emergency room each serve a part of this function for some people some of the time. None is ideally constituted for the job I have in mind. We may have to invent a new institution to do it.

And that invention, or the refinement of existing systems, is very much the business of medical education. As medical education involves itself deeply in the community, new forms and patterns of practice may well develop for bringing the mainstream of American medicine to the people.

It will not be an easy transition. The comfortable certainty of supporting services, to which the hospital physician is accustomed, does not exist outside the walls. But as we move out to meet the health problems of the people, the supporting services will follow. We will learn what kinds of helpers we need and in what numbers, and we will have a setting in which to train them. We will learn how automation can serve in the community setting without violating the human touch that is the heart of medical care.

We have sown the wind with scientific advance and we are reaping the whirlwind of popular expectations. That is the real story of the crisis in medicine and medical education. American medicine is not in a state of decay—far from it. It is doing more things and better for more people than ever before.

But the people whom we serve have accepted the best in health care as a right. They have thrust the challenge upon us. Our response must be to meet them on their own ground.

We shall never have all the physician manpower we need. Therefore we must reëxamine our function as physicians to make sure that we are performing at the top of our professional competence all the time, extending that competence by the use of ancillary personnel.

We shall never have all the ancillary manpower we need either. Therefore we must look to technology, to automation, for all the support they can provide.

Since we shall never be able to remove completely the economic, social and geographic barriers to health care we must do everything possible to surmount those barriers and make equal access to health services more than a pious hope.

Each of these problems has profound implications for medical education—its nature, its content, its orientation and duration. Each is worthy of full treatment by the best minds we have.

But to me the great turning-point of our time—comparable in scope to the union of medicine with science—will be the reorientation of medicine toward the community, turning the physician back toward the people. I am confident that this can be done without sacrifice of scientific excellence; in fact, it must be done if scientific excellence is to yield its full harvest.

Let me conclude by addressing a few words and a few questions to the future physicians in the audience.

A medical degree from Georgetown, or from any of the other great medical schools of our Nation, certifies your scientific competence. You have been prepared, as no generation of medical students before you, to practice medical science. The therapeutic tools at your command would have been beyond the wildest imaginings of those who graduated in Dr. Kober's time.

But the physician differs from the physicist in more than a single syllable. For both, scientific excellence is an indispensable beginning. For the physician, it is only a beginning. There are some quite different questions that I hope each of you will ask yourself as you enter medical practice. Let me start you off with a few, some of them paraphrased from the talk by Mr. McPeak to which I referred earlier, some of them my own.

(*Continued on page 456*)

Transient Normalization of Intraventricular Conduction in Bundle-branch-block*

R. A. MASSUMI, M.D., F.A.C.P.†, AND A. A. TAWAKKOL, M.D.‡

TRANSIENT or intermittent bundle-branch-block (BBB) has been recognized many times since the original description by Sir Thomas Lewis[1] in 1913 and has been reported following postextrasystolic pause[2, 3] and after vagal stimulation with or without slowing of the heart resulting from carotid sinus or eyeball compression.[3-6] It is the purpose of this presentation to report a case in which normalization of intraventricular conduction occurred when the heart was slowed through carotid sinus stimulation and permitted correct interpretation of the underlying myocardial ischemia. Moreover, this report will serve to demonstrate the existence of the incomplete forms of BBB.

Report of Case

A 52-year-old man was admitted to the hospital because of acute dyspnea. Vague "indigestion" and precordial discomfort associated with effort dyspnea and orthopnea had been present for 2 months. He was found to be in severe respiratory distress with a blood pressure of 180/110 and a pulse rate of 90/min. Acute left ventricular failure with pulmonary edema was suspected and confirmed by a chest roentgenogram. It responded promptly to the use of morphine sulfate and oxygen therapy and did not recur during the remainder of the 10 hospital days. The only laboratory abnormality was a serum lactic dehydrogenase level of 1,100 U which returned to normal within a few days. The white cell count and the serum glutamic oxaloacetic transaminase remained normal.

The admission electrocardiogram and those taken during the next 48 hours showed complete left BBB associated with left axis deviation (figure 1-A). Because of the initial presentation with acute pulmonary edema acute myocardial infarction was strongly suspected but could neither be excluded nor confirmed because of the LBBB. The ECG taken on the second day contained premature ventricular beats in leads 1,3 and aVF. The beats immediately following premature beats exhibited normal intraventricular conduction and were therefore suitable for interpretation (figure 1-B). It was observed that normalization of intraventricular conduction could be achieved at will by slowing the heart through gentle massage of the carotid sinus (figure 2-A). It was decided, therefore, to utilize this technique and secure normalization in all 12 leads in order to make accurate interpretations possible. Figure 2-B is the result of this procedure.

The tracing thus completed showed evidence of left ventricular hypertrophy and ischemia. The absence of R deflection in leads V_1 and V_2 suggested a small anteroseptal infarction but was also compatible with left ventricular hypertrophy. On one occasion, as the normalized conduction was returning to the pattern of LBBB, some intermediate forms of QRS (incomplete LBBB) were observed (figure 3-A). Tracings taken on the third hospital day and afterwards showed normal conduction. Since discharge from the hospital the patient has remained free of symptoms.

Discussion

The electrocardiographic evaluation of a patient with suspected coronary artery disease, with or without infarction, is fraught with considerable uncertainty and subjectivity if the intraventricular conduction is abnormal. The difficulty stems from 2 facts. First, the alteration in the sequence of ventricular activation changes the initial and terminal vector forces and either produces "infarction type" Q waves in otherwise healthy areas of the myocardium or, more significantly, wipes out actual infarction Q waves by means of diverting the initial forces toward the left ventricle. Second, the marked ST-segment shifts away from the ventricle whose conduction is delayed and the secondary T-wave changes, both of which repre-

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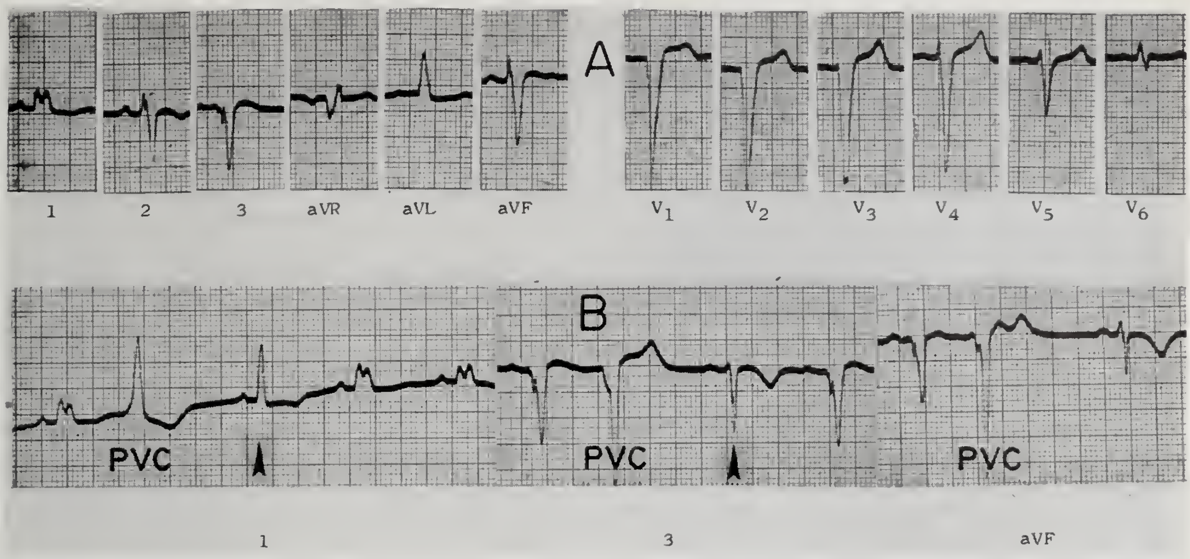

FIG. 1. A. Twelve-lead ECG taken shortly after admission shows complete left BBB. The marked left axis deviation is abnormal even in the face of the LBBB and indicates ischemic or other involvement of the myocardium of the left ventricle and the interventricular septum.

B. Leads 1,3 and aVF demonstrate normalized intraventricular conduction in beats (arrows) occurring after the pause that follows premature ventricular contractions (PVC).

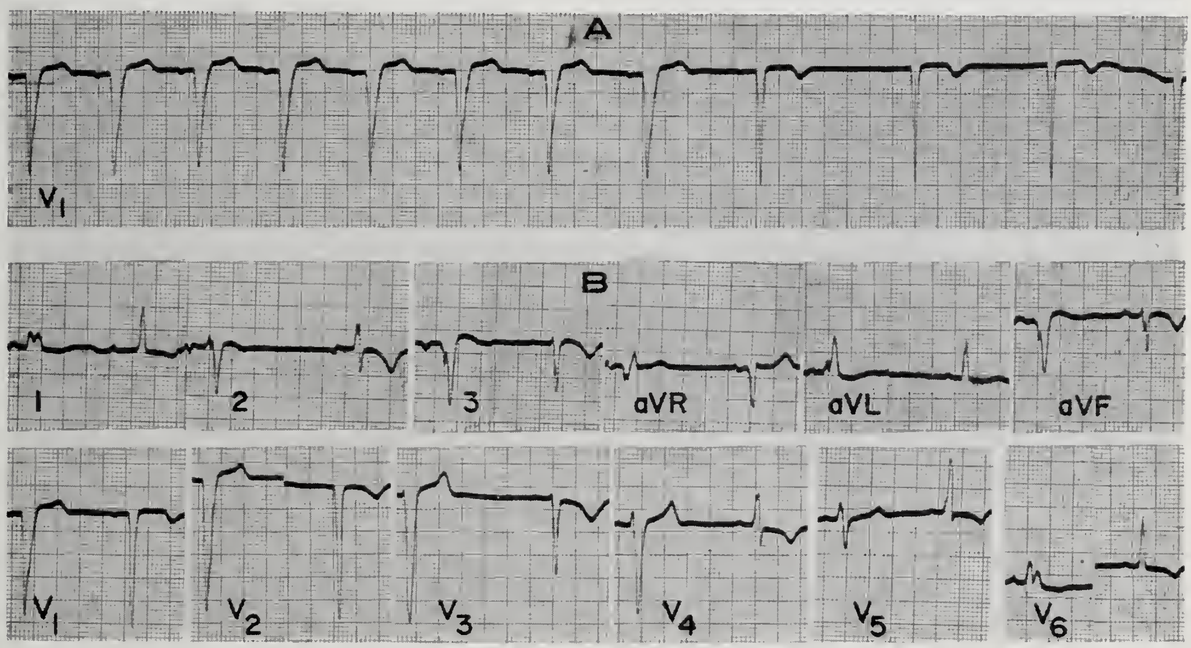

FIG. 2. A. Long strip of lead V_1 depicting normalized intraventricular conduction in the last 4 beats after slowing of the heart was achieved by gentle carotid sinus stimulation.

B. Twelve-lead ECG composed of pairs of beats in each lead. The first beat in each pair shows LBBB and the second beat normal conduction. In most of the leads transition from LBBB to normal occurred within 1 cycle without interposition of incomplete LBBB. Only the right carotid sinus and the right eyeball stimulation possessed the ability to slow the heart and normalize the intraventricular conduction. The normalized beats made interpretation of the tracing and recognition of left ventricular hypertrophy and ischemia possible.

sent asynchronous repolarization of the 2 ventricles, renders interpretation of the injury and ischemic changes virtually impossible, especially if previous tracings are not available. In such cases normalization of intraventricular conduction may be found in postextrasystolic beats or may be induced by gentle massage of the carotid sinus or the eyeball. How frequently it is possible

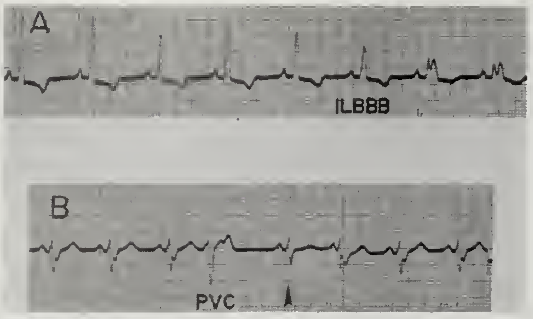

FIG. 3. A. Lead I taken at the time of carotid sinus stimulation showing gradual transition from LBBB to normal with intermediate forms of incomplete LBBB (ILBBB) in which the duration and configuration of the QRS lay between those of LBBB and those of normal intraventricular conduction.

B. Lead 3 in another patient with LBBB. Note normalization of conduction after PVC (arrow). In our experience this phenomenon occurs frequently enough (in about 15 per cent of cases of BBB) to be looked for where ECG interpretation in the presence of normal intraventricular conduction is desired.

to achieve this is unknown, because so far only sporadic reports of 1 or 2 cases have appeared in the literature.[3-6] Our experience with frequent normalization of intraventricular conduction after premature beats in a wide variety of cases of heart disease suggests a figure of 15 per cent success through slowing of the rate (figure 3-B).

The procedure of carotid sinus stimulation with its attendant risks is not justified in every patient with BBB.[7-11] It must be emphasized that only cases presenting significant diagnostic difficulty and important therapeutic choices should be considered for this procedure and then only with adequate electrocardiographic monitoring, facilities, and personnel trained in the procedure of cardiorespiratory resuscitation present at the bedside.

Summary

A case of ischemic heart disease with severe coronary insufficiency complicated by left bundle-branch-block has been described. Accurate interpretation of the ECG tracing became possible when conduction was normalized through slowing of the heart rate by carotid sinus and eyeball compression.

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Traumatic Thrombosis of the Femoral Artery

Report of a Case with Successful Repair and Limb Salvage

JOHN M. KESHISHIAN, M.D., F.A.C.S.*

THE MANAGEMENT of arterial trauma has fallen into certain well-defined methods of treatment.[1, 2] This is due principally to technical advances in arterial and venous reconstruction over the past several years which permit primary restoration of circulation. The unique feature of this case is that it occurred in a child of 9 years of age. A careful review of the literature has not shown a similar case reported, although one may assume that other such cases exist.

Report of Case

DD (7-24-64), a 9-year-old white girl, had been waiting for a school bus when she was struck by a heavy cement mixer truck traveling at a high speed. After jumping the curb, the wheels of the mixer ran over her abdomen and pelvis in an oblique manner from left to right. She was taken to the nearest hospital (Leland Memorial Hospital) in shock and in an unconscious state where resuscitative efforts were begun. She had sustained multiple soft tissue injuries to the body as well as to the extremities and pelvis. After resuscitation it was noted that the right leg was cool and blanched with absence of the pulse in the right groin. In comparison the opposite pulse was present and forceful.

The girl was taken to the operating room for débridement of the injured areas under general anesthesia. After the region of the right inguinal area was cleaned and débrided it was observed that the leg was still cold and devoid of pulses from the groin down. Vascular consultation was requested and it was quickly determined that a major vascular injury existed. The common femoral artery was rapidly dissected out and found to be firm, bluish and pulseless. Dissection was carried upward and downward until the external iliac artery was identified. The external iliac artery was in spasm, but a pulse was easily transmitted through it. A small needle was inserted, and aspiration yielded a free flow of blood. Dissection was carried down further until a good femoral artery could be felt. The injured part of the artery had been very badly traumatized and appeared to have sustained a "grinding" type of blunt trauma (figures 1 and 2). There was rupture of the adventitial coat with a trapped hematoma beneath.

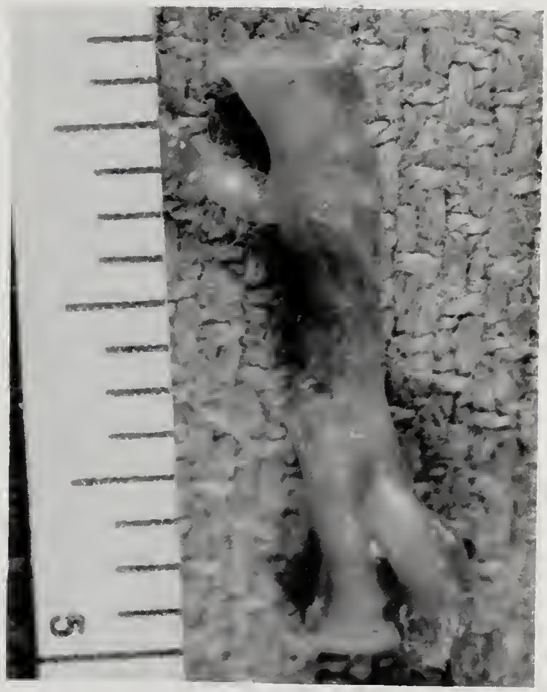

FIG. 1. External view of the damaged femoral artery. Note the central area of tissue destruction. The adventitial coat has been destroyed. The small branch in the upper right hand side has had disruption of the intimal continuity.

N.B. The specimen shown here is considerably shrunken from its original state.

The artery was opened in a longitudinal direction, and a firm thrombus was found beneath the intimal layer. The traumatized area measured 2 cm. It was deemed too wide a gap for end-to-end anastomosis and too risky for a plastic prosthesis in the presence of contamination. The choices were ligation of the ends of the artery or attempting an autogenous venous graft. The latter was decided upon, and the ipsilateral saphenous vein removed and readied for transplanting. The vein was in spasm and appeared to be alarmingly small in diameter. Nevertheless, by gentle irrigations with saline and removal of extraneous areolar tissue and with hydrostatic dilation, a vein diameter of 4 mm. was obtained. This was then interposed in the gap with interrupted sutures of 6-0 ophthalmic silk. As the graft was being sutured in place it was bathed in a 2 per cent Xylocaine® solution with the hope of preventing operative and postanastomotic spasm. After the anastomosis was completed and the clamps removed a forceful pulse was obtained in the distal artery and the graft appeared to be functioning satisfactorily. The wound was generously irrigated and closed loosely in layers. Shortly after the operation was terminated the extremity "pinked up" and had good venous filling. Capillary filling time had returned to normal in the toes and nailbeds.

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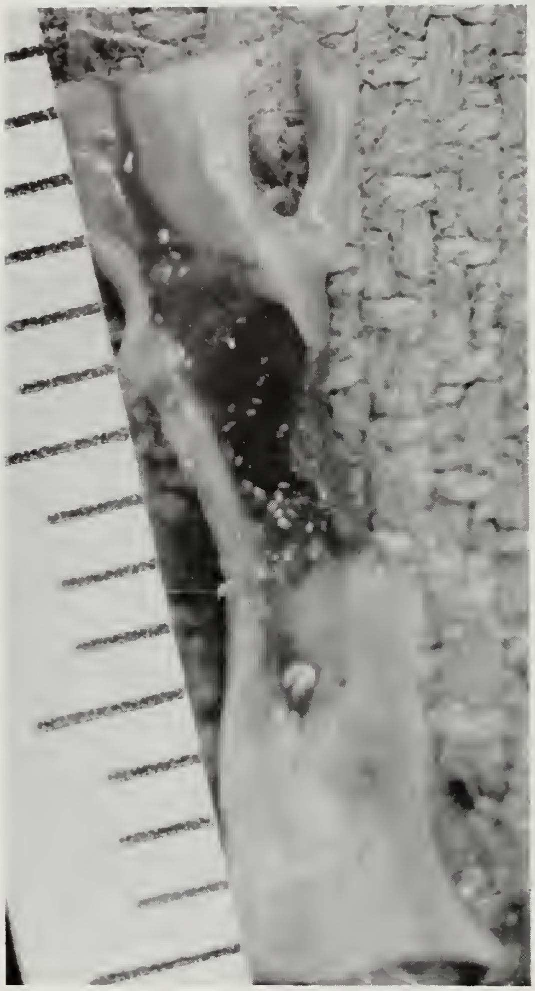

FIG. 2. Internal view of artery. The intimal disruption is clearly seen in the central portion. The large thrombus was completely occluding and was both epi- and subintimal.

After a protracted course involving numerous plastic procedures for other injuries the patient made a satisfactory recovery. Other plastic operations to the perineum will be performed. She has since returned to school and is playing with her schoolmates. The graft has remained patent for over 2 years as evidenced by a forceful pulse in the groin, in the popliteal, and in the dorsalis pedis arteries. Arteriograms have not been performed and none is contemplated at the present time.

Discussion

There are 2 critical periods for vascular prostheses. The first is in the immediate postoperative period, and the second is at a period arbitrarily chosen as being somewhere between 18 and 24 months after the operation. In the first instance the immediate postoperative period is fraught with dangers of clotting due to associated undetected injuries distally, undetected obstructions to runoff, or to significant drops in arterial tension which permit stagnation and clotting. One of the problems most insidious and difficult to detect is arterial spasm in the traumatized extremity. This may be a manifestation of sympathetic overactivity and, if present, should be treated with concomitant sympathetic block or ipsilateral sympathectomy. Another dangerous interval is the immediate postoperative period while patients are being transferred from the operating room to the recovery room. Here blood pressure drop may develop and, if this is not quickly remedied, thrombosis of a delicate piece of technical work may occur. The arbitrary period of 18 to 24 months seems to be a magic figure arrived at by surgeons when evaluating dacron prostheses. In past years it was noted that most dacron prostheses (60 per cent) would become occluded in 24 months. This figure has not always been agreed upon by vascular surgeons, but in general the majority have indicated this to be the significant time period. I have delayed reporting this case until such time period had elapsed.

In past years, especially prior to World War II, arterial ligation was the most common method of handling severe arterial trauma involving large vessels. On the contrary, today efforts are made at arterial reconstruction in cases which are almost beyond hope. In a surprising number of instances temporizing effects or satisfactory results have been obtained. Although children survive ligation of major extremity vessels, it is probably better to attempt reconstructive measures if an opportunity permits. Unquestionably this case would have led to gangrene and loss of the extremity had con-

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Transient Atrioventricular Block Induced by Respiration*

MAIDUL ISLAM KHAN, M.D.†, JOHN B. JOHNSON, M.D., F.A.C.P.‡, AND CHARLES HARRISON, M.D.§

ALTHOUGH HEART MUSCLE has its spontaneous rhythmicity, the heart rate and atrioventricular conduction are under autonomic nervous control through numerous reflex mechanisms.[1] The cardiorespiratory reflexes play a significant, though not fully understood, role in the regulation of the rate of the pacemaker and of A-V conduction. There are few reports in the literature of atrioventricular block precipitated by respiration. Lamb et al[2] reported various significant cardiac arrhythmias induced by common respiratory maneuvers. These authors, while reporting their experience with special tests to determine the susceptibility of Air Force personnel to syncope, reiterated the importance of respiratory maneuvers in inducing cardiac arrhythmia.[3, 4, 5] The frequency with which cardiac arrhythmia occurs spontaneously with respiration is not known.

The purpose of this paper is to report a case in which palpitation and dizziness could be traced to atrioventricular block induced by respiration in a young woman ostensibly free of organic heart disease.

Report of Case

J. T., a 33-year-old Negro woman, was admitted to the hospital on April 1, 1965 because of episodes of "slow irregular heart beat and occasional dizziness." During the 3 years prior to this hospitalization she had had frequent episodes of "slowed pulse" and "irregular heart beat." On several occasions she had counted her pulse rate at 38 per minute. These frightful "attacks" usually occurred at night when she was in bed, although at times she had experienced them during the day while at work. There were no known precipitating factors. The patient was not taking any medications. Walking and moving about would give her relief with increase in heart rate. On several occasions she felt dizzy during the attacks but had no syncope. The past history was not remarkable with reference to heart disease. The patient had 1 brother with a lifelong history of a heart murmur who died of congestive heart failure secondary to bacterial endocarditis.

Physical examination showed a well-developed and well-nourished woman with a blood pressure of 124/60 mm.Hg, a pulse rate of 68 per minute, and a normal temperature. Right and left carotid sinus massage failed to slow the heart rate. The heart was not enlarged and showed no heaves or thrills. A short early systolic murmur, grade 1/6, was heard over the apical area. There was no hepatomegaly and no edema.

Hemogram, urine examination, fasting blood sugar, blood urea nitrogen, serologic test for syphilis, and T_3-uptake of red blood cells were all normal. Chest X-ray films and an esophagogram failed to reveal any abnormality in the heart or lungs. Venous pressure and arm-to-tongue circulation time were normal. The initial electrocardiogram showed first degree heart block.

Several days later, without therapy, the electrocardiogram was normal in the supine position with ordinary quiet respiration. Carotid sinus pressure and cigarette smoking produced no abnormality. However, when the patient held her breath in deep inspiration, sinus slowing and first and second degree heart block were produced (figure 1). This abnormal response could be prevented by the intravenous administration of 0.88 mg. of atropine sulfate. The patient was discharged with a diagnosis of transient atrioventricular block, etiology undetermined, with no definite evidence of organic heart disease.

The patient was reëvaluated 7 months later. She had been free of the attacks. This time she showed persistent first degree heart block in the recumbent position during normal quiet respiration. She was subjected to various respiratory maneuvers both in supine and standing positions. The results are shown in table 1. It is apparent that deep inspiration followed by breathholding depressed A-V conduc-

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tion, resulting in second degree heart block, whereas carotid sinus pressure and deep inspiration without breathholding only produced further prolongation of the PR interval. Hyperventilation abolished the heart block and raised the heart rate slightly. With the Valsalva maneuver the PR interval gradually shortened from 0.26 sec. to 0.16 sec., but during the recovery period following this maneuver the PR interval gradually increased resulting in the Wenckebach phenomenon.

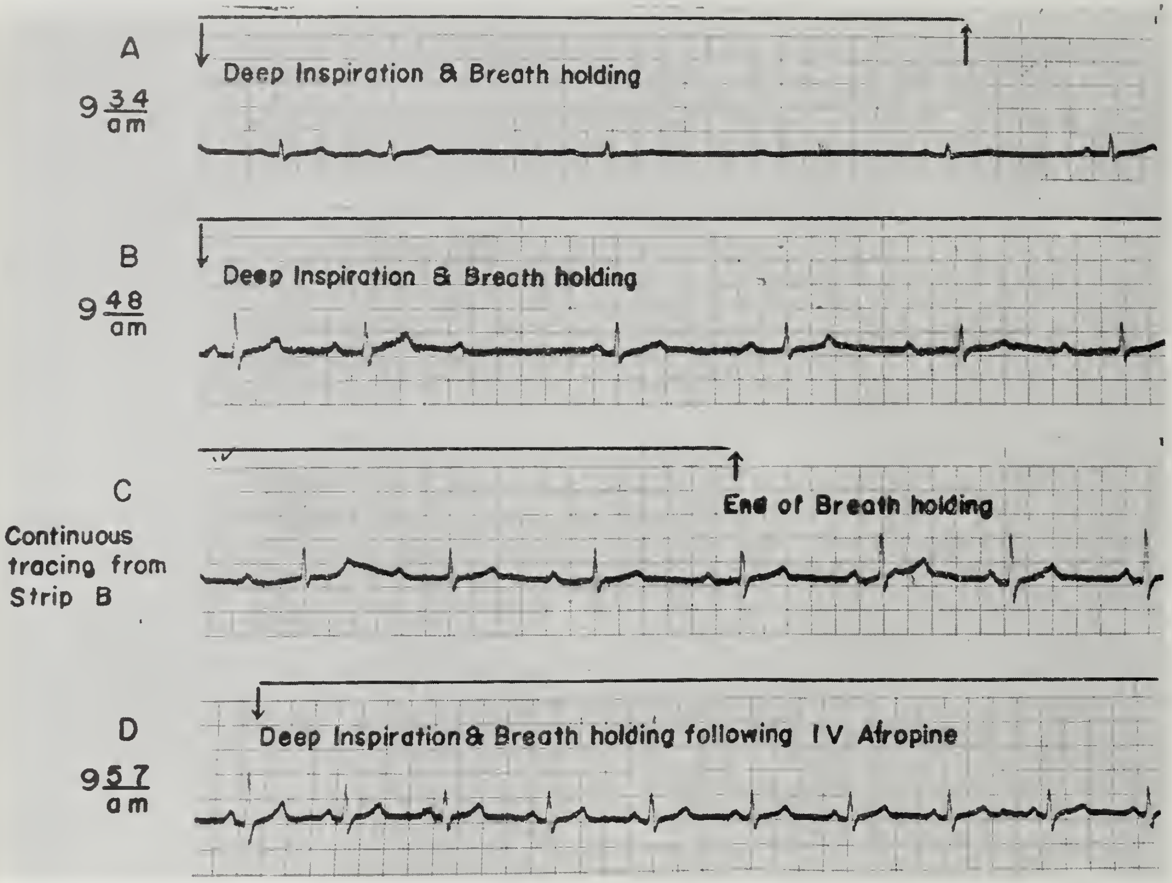
A
9 34/am
Deep Inspiration & Breath holding
B
9 48/am
Deep Inspiration & Breath holding
C
Continuous tracing from Strip B
End of Breath holding
D
9 57/am
Deep Inspiration & Breath holding following IV Atropine

FIG. 1. Effect of deep inspiration and breathholding on cardiac mechanism and disappearance of block following atropine administration: A—sinus slowing and first degree and second degree A-V blocks on deep inspiration with breathholding; B and C—continuous tracings showing sinus slowing and various degrees of A-V block on deep inspiration with breathholding and return to normal conduction with resumption of normal breathing; D—normal A-V conduction with the same respiratory maneuver 9 minutes later, after I.V. atropine.

Discussion

Although the effect of respiration on the rate and rhythm of the heart is variable in different individuals, the waxing and waning of the heart rate with respiration is well known.

Wilson[6, 7] reported cardiac slowing, downward shift of the pacemaker, A-V nodal rhythm, and A-V dissociation during forced expiration in subjects with heart disease. Matthews and Wood[8] reported similar changes produced by voluntary hyperpnea. Varying degrees of A-V block and other arrhythmias have been reported in Cheyne-Stokes respiration, including cardiac standstill with each period of hyperpnea.[9, 10] Hypoxic carotid sinus chemoreceptor stimulation has been postulated as initiating the reflex vagal stimulation in the arrhythmias associated with Cheyne-Stokes respiration. Atropine abolishes this arrhythmia without altering the respiratory abnormality. Hypoxia and the resultant inhibition of the sinus pacemaker may permit a latent ectopic focus to gain control of the heart resulting in serious arrhythmias.

The cardiac arrhythmias induced by respiratory maneuvers, especially breathholding with the patient in the upright position, reported in healthy young adults by Lamb and associates,[2] include sinus arrest, varying degrees of A-V block, and others, all of which could be prevented by atropine. In some instances the induced cardiorespiratory arrhythmias lead to syncope even with the subject recumbent.

Stimulation of stretch receptors located in the tracheobronchial tree, pulmonary parenchyma and pleura have been demonstrated to result in reflex cardiac slowing via the vagus in dogs.[11] It has been postulated that the arrhythmias produced experimentally in man by respiratory maneuvers represent cardio-inhibitory reflexes initiated in the pulmonary stretch receptors and mediated by vagal visceral afferent fibers to the medulla and via vagal efferent fibers to the sino-atrial and atrioventricular nodes.[4]

TABLE 1: Influence of Respiratory Maneuvers on A-V Conduction

MANEUVERS	POSITION OF PATIENT	HEART RATE PER MINUTE	P-R INTERVAL IN SECONDS	CONDUCTION MECHANISM
Control	Supine Standing	68 68	0.26 0.26	First degree A-V block
Right carotid pressure	Supine Standing	68 72	0.32 0.32	First degree A-V block
Left carotid pressure	Supine Standing	68 72	0.36 0.40	First degree A-V block
Valsalva Recovery period	Supine	68	0.16	Sinus rhythm Wenckebach phenomenon
Valsalva	Standing	72	0.18	Sinus rhythm
Deep inspiration	Supine Standing	68 75	0.32 0.18	First degree A-V block Sinus rhythm
Deep inspiration and breath-holding	Supine Standing	52 62	variable variable	Second degree heart block Second degree heart block
Hyperventilation for 1 minute	Supine Standing	72 88	0.19 0.12	Sinus rhythm Sinus rhythm

The underlying mechanism in our patient is obscure. We were unable to demonstrate evidence of organic heart disease. In the initial study with quiet normal breathing the PR interval was normal, yet on other occasions the PR interval with normal breathing was prolonged. It appears, therefore, that the patient may have persistent overactivity of the vagus which is diminished by standing and hyperventilation and aggravated by breathholding in deep inspiration. Under the latter circumstances it is postulated that the pulmonary stretch reflex produces an exaggerated cardio-inhibitory response resulting in the second degree heart block observed.

Whether this mechanism was operative in this patient during the attacks which are described could not be ascertained.

Transient arrhythmias induced by respiratory maneuvers in studies of flying personnel have been shown to have no predictive value in distinguishing between persons with a history of syncope and those without.[3] We have found no evidence in the literature to indicate that such subjects subsequently have any greater tendency to develop organic heart disease than other subjects who have no such transient arrhythmias.

It may be of practical importance to be aware of the possibility of A-V block induced by respiratory maneuvers. Overdistention of the lungs as in underwater swimming and diving and breathholding for other reasons should be avoided in individuals with powerful cardio-inhibitory respiratory reflexes. If at any time positive pressure breathing becomes necessary in therapy or during anesthesia such patients should be protected with atropine.

Summary

A case of transient atrioventricular block related to respiration in a patient apparently free of organic heart disease has been described. Breathholding in deep inspiration was demonstrated to result in second degree heart block. Following the Valsalva maneuver the Wenckebach phenomenon was noted. The exact explanation of this arrhythmia is obscure. It is postulated that increased vagal tone and susceptibility to cardio-inhibitory response acting through pulmonary stretch reflex may be responsible for this A-V block.

The significance of respiratory cardio-inhibitory reflexes with reference to overdistention of the lung in underwater swimming, positive pressure breathing in therapy and in chest surgery was noted.

The authors are indebted to Dr. Francis Blackwell for the opportunity of studying this patient.

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(Continued on page 456)

Treatment of Fibrositis and Other Inflammatory Musculoskeletal Disorders with Local Dexamethasone 21-phosphate Injections

A. B. WEIN, M.D.*

Suppressive drug therapy in musculoskeletal inflammations with locally injected corticosteroid preparations is an accepted and effective therapeutic modality.[1-8] The response to this type of therapy in localized inflammatory disorders has often been marked by a prompt amelioration of pain, an increase in the comfortable range of motion, and an earlier return to daily routine.

In addition to a predominantly local action and virtual lack of systemic hormonal effects, therapy with injectable corticosteroids for palliation has provided the physician with a safe and simple means for selectively treating the individually involved joints.[8]

Dexamethasone 21-phosphate,† described elsewhere in the literature,[9-14] combines potent therapeutic activities and unique physical properties. It is approximately 3,000 times more soluble than and possesses twice the half-life of hydrocortisone, presumably accounting for a greater therapeutic efficacy. Because of these attributes it can be administered through a small-bore needle, giving prompt onset of action and favorable therapeutic effect.

The purpose of this communication is to report on the utility of dexamethasone 21-phosphate in the large group of cases comprising local fibromyositic and other musculoskeletal disorders, demonstrating ease of administration and therapeutic effectiveness.

Methods and Materials

In this series of 101 patients there were 36 males and 63 females, varying in age from 10 to 84 years. Two patients were excluded from final evaluation because of incomplete data. Of the remaining 99 patients 75 had fibrositic disorders, including bursitis, tenosynovitis, synovitis, tendonitis and fibromyositis, and the remaining 24 patients suffered from a variety of other musculoskeletal disorders of varying severity (table 1).

Sole treatment for the majority of patients consisted of instillation of dexamethasone 21-phosphate, 4 mg. or 8 mg. directly into the affected area. In some instances injection of a local anesthetic, analgesics and muscle-relaxants, or physiotherapy, were employed concurrently. The size of the dose was determined largely by the nature and extent of the condition, the size of the joint involved, and the physician's judgment. The concurrent use of local anesthetics was, in a majority of instances, intended to overcome the patient's fear of the needle and to help localize the site of inflammation. The latter was determined by the patient's subjective response, a feeling of relief from pain. This response served to assure the physician that the medication had been instilled in the exact area of trouble. In a few instances local anesthetics were employed as a palliative for extremely painful swollen joints.

All patients under treatment were required to return to the treatment center at specified intervals, which varied from 1 to 7 days, for evaluation of progress. This was determined by measuring the size and range of motion of the affected joints, and evaluation by patient and examiner of the degree of pain and tenderness. The patients were given additional injections, physiotherapy, or other adjuvants if the situation so required. They were asked to evaluate the effects of treatment in terms of ability to perform routine tasks, either at home or on the job, and were also asked questions intended to elicit remarks pertaining to untoward effects of the medication. These data were recorded on special case report forms. All of the patients who did not completely resolve their difficulties

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† Supplied as Hexadrol® Phosphate Injection by Organon Inc., West Orange, New Jersey.

TABLE 1: Diagnoses of Patients Treated
36 Males, 63 Females, Ages 10–84

Diagnosis	No. Patients
Bursitis	
Knee	18
Shoulder	8
Elbow	3
Heel	3
Foot	1
Hip	1
Neck	3
Back	1
Spine	1
Scapula	1
Tenosynovitis	
Shoulder	1
Ankle	4
Wrist	2
Feet	3
Knee	1
Tendonitis	5
Synovitis	
Knee—traumatic	7
Knee	6
Feet	1
Ankle	2
Fibrositis	
Calf muscle	1
Back	1
Perostitis	
Rib	1
Miscellaneous	
Acromioclavicular joint degeneration	11
Chondromalacia—knee	3
Tendon avulsion—wrist	2
Internal derangement—knee	1
Osteochondroma—femur	1
Sprain—shoulder	1
Calcification—foot	1
Fibrous fatty tissue—left second toe	1
Hemarthrosis—knee	1
Arthritis	2
Total	99

with medication were eventually referred to surgery. Generally the duration of treatment in terms of the number of injections varied from 1 to 12, the majority of patients receiving 1 or 2 injections.

Injection Techniques

In preparing each of the patients for injections, the point of greatest tenderness or certain anatomical landmarks were located. The site for the introduction of the needle was then carefully sterilized with an antiseptic, marked with iodine and then entered. For injections which were not intra-articular it was hardly possible to accomplish distribution of medication by way of a single puncture. In these cases multiple puncture techniques were employed to instill the medication into a number of sites for optimal effect. This technique was frequently employed when treating more diffuse conditions such as tendonitis, peritendonitis, fibromyositis, etc. After the medication was instilled, the needle was withdrawn, a firm pressure was maintained on the puncture site for approximately 60 seconds, and then an adhesive bandage was applied. The patients were then cautioned against overuse of the affected joints. Where multipunctures were used, patients were provided with some form of analgesic medication to counter any painful reaction resulting from the drug-tissue interaction. Large-bore needles were seldom employed because of the free-flowing nature and solubility of the solution. The size of the needles used was 25-gauge for small areas and 22- or 23-gauge for larger areas.

Based on my experience, 3 areas noted below have been most frequently treated in this office. The following techniques have been largely responsible for favorably influencing the patient's response to the medication. These techniques involve the instillation of medication into the bicipital tendon, the acromioclavicular joint, and the bursa in the area of the collateral ligament of the knee.

In bicipital tendonitis, with the patient in a recumbent, supine position and the upper extremity held in external rotation by an assistant, the location of the tendon is determined by repeated thumb palpation. When the point of greatest tenderness is defined the patient will usually respond with a grimace or a pain reaction. The entire area of tenderness is then cleaned with an antiseptic and 4 mg. to 8 mg. injection of dexamethasone 21-phosphate is instilled into this area with multiple puncture injections with a 22- or 23-gauge needle. This treatment is repeated at intervals of 2 to 3 days until the condition is resolved.

In preparing a patient for injection of the acromioclavicular joint the area is palpated with the patient seated and his arms hanging down. Quite often localization of the joint may be difficult because of degenerative changes which have brought about narrowing of the joint. In such instances an X-ray film may be of considerable value, particularly if it shows an opening into which a needle may be inserted. An occasional ridge, usually associated with hypertrophic arthritis, can also serve as a landmark. If some doubt exists concerning the exact location of the joint, multiple injections of a local anesthetic into the skin and superficial tissues around the involved area are of considerable help in locating the entrance to the joint.

For treating bursitis of the medial collateral ligament, the patient is placed in a recumbent supine position and the knee is flexed and extended. The point of greatest tenderness, determined by repeated thumb palpation and the patient's reaction to pain, is usually located at a point midway between flexion and extension. After the area is identified it is cleansed with an antiseptic. Dexamethasone 21-phosphate is administered concurrently with a local anesthetic with multipuncture instillations, covering an area of approximately 2 cm. in diameter. This treatment is repeated every 2 or 3 days.

Results

The response to treatment, detailed in table 2-A, was exceptionally favorable in the majority of patients treated. Good to excellent results were reported for 85 patients and fair to poor results for 14 patients. In the latter group total treatment failure was reported in 2 patients. One of the patients had a degenerated acromioclavicular joint which required surgical treatment, the other had fibrous fatty tissue of the second left toe which did not improve with treatment. The onset of relief was noted to occur within 6 hours in 59 patients and within 24 hours in the remaining patients (table 2-B).

Toxic manifestations attributable to the medication or demonstrable evidence of pain as a result of treatment were absent throughout the study.

Seventeen patients were regarded as candidates for surgery prior to injection therapy. The exceptionally good response in 3 patients with degeneration of the acromioclavicular disc and in 2 with chondromalacia patella obviated the need for surgical intervention. In 12, however, where transient benefit was derived, surgery was still considered. Five of these 12 patients, 2 with acromioclavicular disc degeneration, 1 with subacromial bursitis and possible disc injury to the acromioclavicular joint, 1 with acromioclavicular bursitis and degenerative arthritis, and 1 with internal derangement of the knee with hemarthrosis, have already had surgery. In the remaining 7 patients surgery was postponed, at least temporarily, because of response to the medication. This latter group included 3 patients with degeneration of the acromioclavicular joint, 3 with bursitis (shoulder, cervical spine and olecranon bursa), and 1 with synovitis of the knee (table 2-C).

The data in this study (table 2-D) also reveal that 38 patients received single injections of either 4 mg. or 8 mg. of the medication; 30 received 2 injections; 17 received 3 injections; and 14 received 4 or more injections. The total number of 4 mg. and 8 mg. injections were 67 and 32 respectively. In 36 instances a local anesthetic was administered in conjunction with the medication to help the patient overcome his fear of the "needle," to help pinpoint the precise area of the lesion, and, in a few instances, to help quiet the painful, hot and swollen joints. Physiotherapy was added to the treatment regimen in 19 patients. Other adjuvants included a muscle relaxant in 1 patient with bursitis of the knee and an analgesic agent in 1 patient with bursitis of the neck.

A closer look at the results obtained in terms of the number and size of injections with and without concurrent administration of a local anesthetic is provided in table 3. These data serve to point up the lack of any significant differences in response of patients receiving medication with or without a local anesthetic. Of further interest are the data presented in table 4 which strongly suggest the lack of correlation between the age of the patient and his response to medication.

TABLE 2: Response to Treatment

A. Response to treatment—99 patients

Excellent	Good	Fair	None
55	30	12	2

B. Rapidity of response—99 patients

Less than 6 Hours	6–24 Hours	More than 24 Hours
59	40	0

C. Patients in whom surgery was regarded as likely—17

Need for Surgery Obviated	Surgery Postponed	Surgery Performed
5	7	5

D. Number of injections (4 mg./8 mg.)—99 patients

1	2	3	4 or More
38 (29/9)	30 (18/12)	17 (12/5)	14 (9/5)

TABLE 3: Results According to the Number of Injections With and Without a Local Anesthetic

No. Injections (4 mg.)	Excellent		Good		Fair		None	
	W*	Wo†	W	Wo	W	Wo	W	Wo
1	7	10	3	4	1	1	0	0
2	3	7	4	1	0	1	0	0
3	1	4	4	1	1	2	0	0
4+	1	2	1	1	1	0	0	0
Total	12	23	12	7	3	4	0	0
(8 mg.)								
1	1	7	1	3	0	0	2	0
2	1	6	0	2	0	2	0	0
3	1	1	1	1	0	1	0	0
4+	1	2	0	3	1	1	0	0
Total	4	16	2	9	1	4	2	0

* W—Dexamethasone 21-phosphate with local anesthetic.

† Wo—Dexamethasone 21-phosphate only.

Discussion and Conclusion

Injectable dexamethasone 21-phosphate was administered to 99 patients afflicted with fibrositic and other musculoskeletal disorders of a localized nature. Administered in doses of 4 mg. to 8 mg., sometimes in conjunction with injections of a local anesthetic, dexamethasone 21-phosphate yielded good to excellent results in 85 patients, fair results in 12, and no results in 2. It completely obviated the need for surgery in 5 and postponed it in 7. Onset of relief was rapid, occurring within 6 hours in 59 patients and within 24 hours in the remaining patients. Evidence of pain or toxic effects attributable to the medication was not observed in any of the patients in this series.

For the busy physician who encounters a variety of musculoskeletal disorders in his daily practice local injection of dexamethasone 21-phosphate is a therapeutic procedure of considerable value. The medication is highly soluble, flowing easily through a needle. It does not crystallize, hence it is easy and painless to administer, even through a small-bore needle. A small amount, usually 4 mg. or 8 mg., usually suffices to produce a favorable therapeutic effect which often becomes manifest within 30 minutes to 3 hours and persists for several days. In most instances response to dexamethasone 21-phosphate is reflected by a great decrease in swelling and joint temperature, an increase in functional capacity, and a shorter period of disability. With the exception of those patients who were candidates for surgery, the patients in this series have been able to perform normal tasks with minimal discomfort and minimal loss of time from work. In those who were regarded as candidates for surgery, the effectiveness of conservative injection therapy in a significant number of patients was a most gratifying therapeutic result.

TABLE 4: Results of Therapy According to Age

Age Range	Excellent	Good	Fair	None	Total
None given	8	4	1	0	13
10–20	7	1	0	0	8
21–30	9	4	2	0	15
31–40	6	7	1	1	15
41–50	10	7	7	0	24
51–60	8	3	1	1	13
61–70	3	3	0	0	6
71–84	4	1	0	0	5
Total	55	30	12	2	99

In the present study several factors were critically examined: (a) ease of administration, (b) rapidity of action, (c) therapeutic effectiveness as measured by number of injections needed and the degree of relief from symptoms, and, finally, (d) the effect on patients in whom surgery was considered. In all these areas local injection of dexamethasone 21-phosphate proved to be exceptionally valuable in patients with musculoskeletal disorders where local steroid effect is desired.

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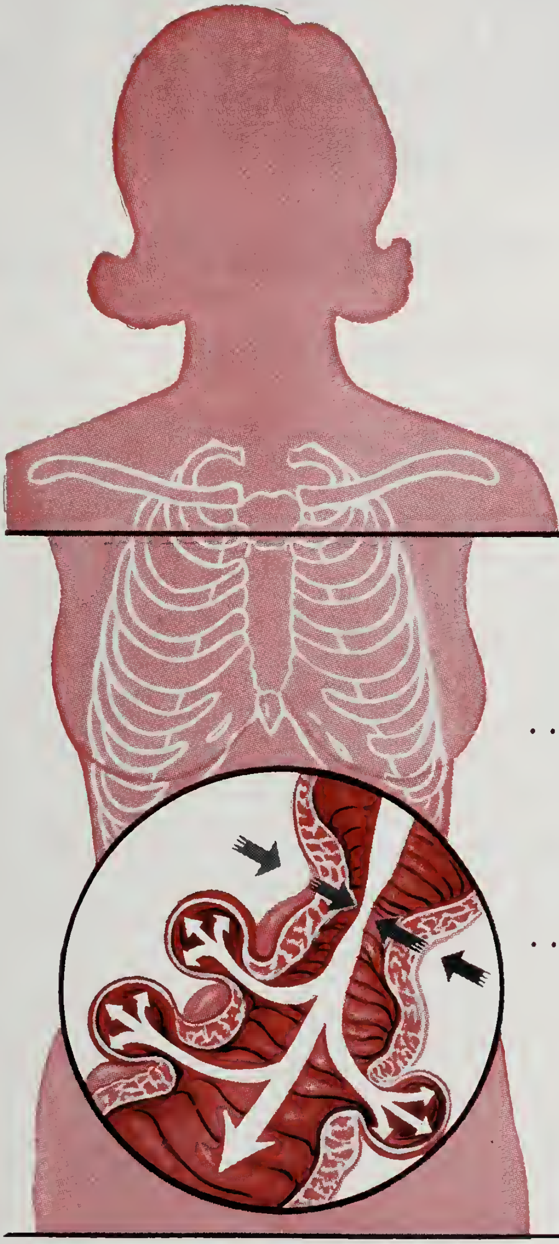

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SEARLE

Research in the Service of Medicine

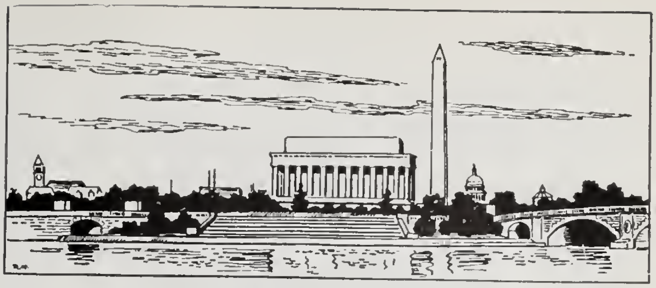
PRESIDENT'S PAGE

DIRECT BILLING OR ASSIGNMENT?

After a brief experience with Medicare it is becoming increasingly evident that one of the features of this law that will be a source of controversy is the mechanism of billing under Part B of Title XVIII. Two optional methods of payment are provided, the choice resting with the physician. In the first instance, the bill, representing a reasonable and customary fee, is paid in full by the patient, receipted by the physician, and in turn the patient submits this to the carrier for the payment, which is ordinarily to the extent of 80 per cent of the total fee. The only requirement involving the physician in this first alternative is some degree of itemization of his services. The other method is one of assignment: after producing evidence that he has already paid the $50 deductible amount or actually pays it as a part of the submitted bill, the patient pays the physician 20 per cent of the reasonable and customary fee, and in the designated space on the Medicare form indicates by his signature that he is assigning the fee to the physician; the physician in turn completes his portion of the form, which calls for an itemization of services, and submits it to the insurance carrier for 80 per cent payment.

While it has been suggested by some that the insertion of these alternatives in the composition of this legislation was a devious device to entrap the physician into an awkward public relations posture, it is reasonable that the alternate method of assignment was devised for those individuals who are unable to pay in cash any substantial medical fee. In most cases the direct payment billing method would seem to be preferable in that it appears to maintain a closer and more intimate patient-doctor relationship. However, after reading the series of articles on Medicare by a staff writer of one of our local papers, I realize that it is being interpreted in some quarters as an opportunity for the physician to charge an excessive fee which the disillusioned patient finds later is covered only in small part by Medicare benefits. This accusation I believe is ill-founded and grossly unfair; the submission of reasonable and customary fees has been the practice of members of our profession for centuries. It goes without saying that in those instances in which it would constitute a hardship for the patient to pay the bill directly, acceptance by the physician of an assignment is warranted. While administration spokesmen seem to prefer this latter method of payment, it does place on the physician the onus of bringing to the patient's attention the disillusioning news that he has to pay a sizable amount of the bill himself.

Robert J Coffey



EDITORIALS

The Foreign Physician in the United States

The large number of foreign physicians in graduate training in American hospitals is a source of concern to their governments and also to directors of training programs in this country. The foreign country is unhappy about a program which further depletes its number of physicians. The young physicians who come to the United States may never return to their homeland. Furthermore, some of those who do return are not trained for the problems they will face at home.

What is the real purpose of appointing foreign graduates to our training program? Those who have worked with these physicians recognize a marked difference in the fluency and medical background of students from foreign countries. These differences are not found to the same degree in graduates of United States medical schools. However, we are pleasantly surprised to note the remarkable adaptation to American medicine of so many foreign students. American students who work with them begin to appreciate their intelligence and dedication.

Just as they adapt themselves to our medicine, many become Americanized in other spheres. The problem pointed up by Dr. Hunt* begins to mount. The desire to return home wanes with each passing year as the student develops roots, perhaps marries. Others have long planned to leave home for the United States or Canada at the first opportunity. This is not a great plot or master scheme; it is merely the attraction of American life and medicine to intelligent young physicians. Some in training here are aware that the economy of their country is not ready to support the type of medicine they have been practicing. The need for food, shelter, sanitation, and preventive medicine must be met before there will be any place for sophisticated diagnosis and therapy. For others, from more established countries, the attractions may be the same as for all immigrants to this country.

It is doubtful that a completely satisfactory solution can be found. Are we to make America less attractive to immigrants? Students on Exchange Visitor Programs should be encouraged to return home, but this is the responsibility of the State Department. However, what will prevent them from applying later for an immigrant visa?

Some foreign graduates find themselves in poor programs, and others who may be in good programs have few American graduates as associates. The lack of contact with American graduates detracts from the value of the educational experience.

To properly evaluate teaching programs requires a much larger staff than the AMA Council on Medical Education can provide. Therefore, only minimum standards can be assured.

The medical profession should be more concerned with the selection of applicants and their placement in programs which will prepare them for practice at home. This would require a selection committee in each country to present qualified candidates to a placement service in this country, perhaps under the direction of the Association of American Medical Colleges and the Council on Medical Education of the American Medical Association. The World Health Organization might consider this a worthwhile project. The candidate could then be assigned to a program for which he is qualified, which meets his needs and those of his country. In time, exchange programs involving American graduates in foreign countries could evolve.

The present competition for interns and resi-

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* See pages 441–442 in this issue.

Opinions expressed in contributions to the Editorial Section are those of the writers and do not necessarily reflect the views of the Medical Society of the District of Columbia

dents is as keen in the university hospitals as it is in the non-university hospitals. It is less obvious because most university programs fill their quotas with American graduates, but each is trying to attract the first-rate graduates. There are few foreign graduates appointed to internship in these hospitals. Any program to incorporate foreign students into the stronger universities at the intern or resident level requires a willingness on the part of all the universities to coöperate in the Exchange Visitor Program. Approved non-university hospitals could also participate either independently or in affiliation.

The present system is a "double-blind" study. The applicant knows little or nothing about the program he has selected by mail. The institution has little real knowledge about the applicant. The fact that it has worked fairly well in so many instances is a tribute to the good will of both.

We should, then, be encouraged to follow Dr. Hunt's suggestions of an organized approach.

If the program has worked at all under the worst of circumstances, what might it do under the best?

James A. Curtin, M.D.
Director of Medical Education, Washington Hospital Center

What Is an Emergency?

What is an emergency? Exposure to measles? Tonsillitis? A short supply of "The Pill" in the middle of a long weekend? "Emergency" has become one of the most imprecise and overworked words in the medical lexicon. For the sanity of the medical profession this catch-all should be redefined and the public educated to understand the meaning of a real medical emergency.

Recently an "emergency autopsy" was scheduled at Suburban Hospital in Bethesda, Md. The head nurse and I agreed that if an autopsy is indicated chances are the emergency is over. This was unusual. But "Wolf, wolf!" calls from the public are becoming more and more an every-day occurrence. Druggists get "emergency calls" for prescription refills on diet depressants. The local volunteer ambulance squad responds to calls in the night to "rescue" a child with tonsillitis. And, as everyone knows, our hospital Emergency Rooms are treating routine medical problems from headaches to poison ivy. The night I was awakened by a call from the Emergency Room concerning a young woman who was there for constipation, I decided to write this piece.

The style of life today, when so much is accomplished by the flick of a switch, seems to breed an attitude which expects instant action on any demand. Being human, physicians can't respond immediately every time the bell rings. Most of us require some rest and recreation in order to function efficiently at work. The people who staff the Emergency Room of a busy hospital are human too. If their special skills are to be dissipated supplying aspirin and band-aids to anyone who drops in they can't give proper attention to heart failure or hemorrhage.

Some time ago a caller whom I'd never seen requested an "emergency smallpox vaccination." He was pretty upset when he learned we didn't generally treat routine injections as emergencies. This man had to leave for London in 3 hours and to him getting that vaccination was an emergency. But medical emergency? No.

The dictionary defines emergency as an "unforeseen happening or a state of affairs requiring prompt action." Granted, the above examples under certain circumstances could fill this criterion, but it is obvious that we need a term to distinguish a personal emergency from a real medical emergency. Severe wounds, laceration, abdominal pain and bleeding, fracture, loss or change of consciousness, cardiac arrest, hard labor, overdose of medication, and possible poisoning would all be in the category of "a state of affairs requiring prompt action." Surely an "unforeseen happening" such as any of these requires mobilization of medical facilities in quite a different way from that required by headache, mild fever, most contagious diseases, sore throat, cold, constipation, prescription renewal, and vaccination. A medical situation that is grave and urgent as opposed to one that is merely uncomfortable and inconvenient should be termed "life-threatening." If our aides and answering-service operators were trained to understand and make this distinction the medical doctor would see far fewer "emergency cases." Certainly, the midnight emergency call for the cold that has to be cured by the weekend could be rescheduled for daytime care.

Physicians and our paramedical colleagues are somewhat to blame for the overworked "emergency" misnomer. At night and on weekends many of us take only real emergency calls. Obviously, at these times if someone wants a doctor for any reason at all and knows this he'll term his problem "an emergency." Moreover, it is difficult to get a rescue squad to respond with hospital transportation unless we call the situation an emergency. A fractured ankle or a plus-minus right lower quadrant pain with nausea requires transportation but not necessarily a 50-mile-an-hour siren-blasting trip to the hospital. This, however, may very well be just what the public wants.

Should we move with the times—blast the siren and send all patients off to the Emergency Room? Or, to meet the increasing demand for emergency attention, should we schedule office appointments from 10:00 p.m. to 1:00 a.m. and house calls from 1:00 to 8:00 in the morning?

Before we have to take this extreme action let's clarify for the public exactly what we consider to be an emergency. Together with our aides, let's help people distinguish between a personal emergency which may be inconvenient and uncomfortable and a medical one which is grave and life-threatening. If this distinction is made, then equipment, training, talent, and time will be available more readily for the state of affairs which does require immediate action—the life-threatening situation—the true medical emergency.

John B. Umhau, Jr., M.D.

Cancer Study of Colon and Rectum

The Ad Hoc Cancer Study Committee of the Medical Society of the District of Columbia, with the aid of a grant from the D. C. Division of the American Cancer Society, is beginning a study of cancer of the sigmoid colon and rectum in coöperation with the District of Columbia hospitals.

Members may recall that a successful study of pelvic malignancies was conducted by the Cancer Morbidity Review Committee from 1958 to 1963.

The new Ad Hoc Cancer Study Committee will schedule open case review meetings periodically and will welcome and encourage the participation of every interested physician. Meeting dates will be posted in hospitals and sent to all physicians requesting meeting notices.

Dr. John F. Potter is chairman of the Committee. Other members are Drs. Henry H. Balch, Irving B. Brick, Alejandro F. Castro, Peter D. Comanduras, Ernest A. Gould, Stafford W. Hawken, Calvin T. Klopp, LaSalle D. Leffall, Duane C. Richtmeyer, Jack E. White, and Theodore Winship.

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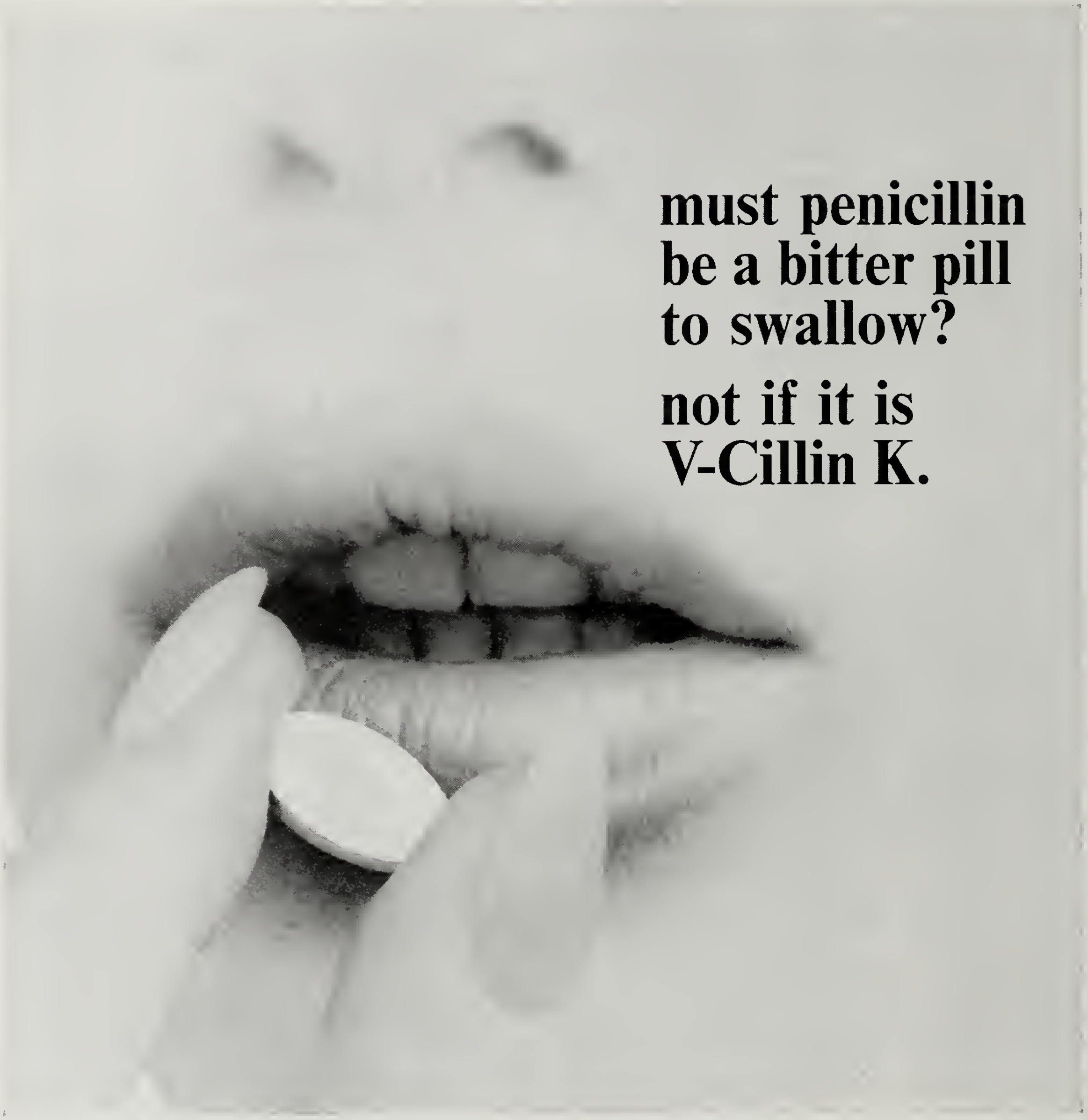

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this issue: emergency anesthesia and the common cold

When emergency anesthesia is complicated by the common cold

Barry Belonsky, M.D., F.A.C.A.
Staff Anesthesiologist, Hospital of The Albert Einstein College of Medicine, New York City

Medical facilities are often presented with unfamiliar patients who have unknown health histories. This is particularly true in emergency situations that arise due to accidents or acute illnesses. These cases may need prompt care requiring anesthesia, and if they involve colds, nasal allergies or other upper respiratory infections, can account for many complications which make up a major hazard during emergency anesthesia.

Administration of general anesthesia to a patient with a cold or upper respiratory infection is a hazardous undertaking. It should be avoided if at all possible. Indeed, the presence of U.R.I. is good reason for postponement of elective surgery.[1] In emergency surgery, regional or local block should be considered, but if general anesthesia is mandatory, it should be approached with utmost caution.

Since the attitude of "emergency surgery — hurry" has been replaced by "emergency surgery — watch out",[2] a knowledge of the complications is a great help in preventing them. Here is a brief outline of the problems involved and their treatment. Prevention of the complications is discussed later.

Complications during the induction of anesthesia

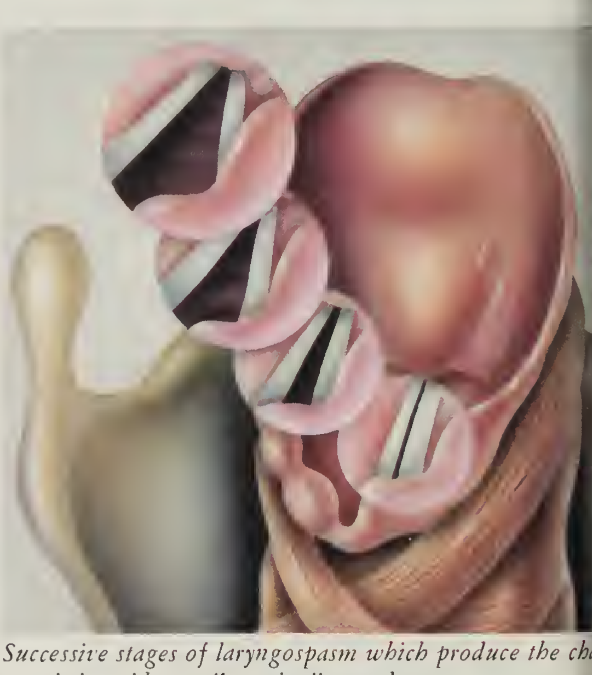
Most of the complications are a direct result of secretions and some a result of accompanying secondary infection. For example, *airway obstruction* due to excessive secretions occurs very commonly and is the direct effect of the cold. Respiratory exchange may be obstructed at any time during anesthesia because of excessive secretions, but is most likely to occur during induction. Suction apparatus must be available to overcome this.[3]

Excess secretions which stimulate and irritate the epiglottis and vocal chords can cause *laryngeal stridor and obstruction*. This can lead to complete laryngeal closure with resultant anoxia and death.

Bronchospasm and laryngospasm can result fror secretions penetrating the bronchi and bronchiole In laryngospasm, there are both inspiratory and e piratory stridor and difficulty in inflating the ches in bronchospasm there is an expiratory wheeze, bu not as much difficulty in inflation, although som resistance may be felt. Stridor is due to partial o complete closure of the vocal cords in spasm and th "crowing" sound is almost pathognomonic.

Secretions obstruct the nasal airways. This produce *difficulty in ventilation* through the mouth until th patient is deep enough to place an oral airway. A intravenous agent can be given to facilitate the i duction of anesthesia.

Difficulties can arise if intubation is performed t ventilate the patient. For example, teeth can b broken by too vigorous attempts at intubation, o the intubation itself may be technically difficult du to secretions obstructing the view of the glottis. Th postoperative sequelae of intubation ranges fro mild laryngitis to pneumonia with atelectasis, an are seen far more commonly in patients sufferin from colds than in normal patients.



Successive stages of laryngospasm which produce the cha acteristic stridor or "crowing" sound.

Progression of bronchioles into bronchospasm.

Complications during the maintenance of anesthesia

Bronchospasm can occur in an unintubated patient due to secretions entering the bronchial tree from above, and acting as an irritant to the bronchi and bronchioles. Secretions accumulate quickly and the patient has to be suctioned continually. The whole cycle of coughing, bucking, laryngospasm and bronchospasm may ensue. The difficult decision here is whether it is better to suction the patient continually or to use an endotracheal tube which protects the cords and bronchi but introduces the risk of attendant complications.

Postoperative complications

Postoperatively, complications can be more serious than even the intra-anesthesia complications, and occur much more frequently in a patient who has been intubated.[4]

Sore throat and pharyngitis can result both from the preoperative upper respiratory infection and from the drying of the mucous membranes which occurs during anesthesia.

Tracheitis and bronchitis often result from secretions trickling down the tracheobronchial tree.

Laryngitis is frequently seen in patients with upper respiratory infections who have been intubated. There is a significant increase in the incidence of laryngitis compared to that in patients without upper respiratory infections.

Subglottic edema is a condition which occurs mainly in children who have been intubated. This pathology results from an exudate developing in the areolar tissue just below the cords. Because of the small size of the child's trachea, even a 1 mm increase in size of the mucous membrane can severely impair the air passage. Children exhibit this by severe expiratory stridor and may even become cyanotic. This may so severely embarrass the child's breathing that it must be treated vigorously. Most authorities agree on the treatment[5,6,7,8] consisting of a high oxygen concentration in the inspired air (60%), plus high humidity (close to 100%). Adequate parenteral fluid intake and slight cooling of the body temperature (by a cooled oxygen tent) also help in mild cases. In severe cases, there may be hypoxia which increases the restlessness and the oxygen demand rises. Sedation is often necessary, although concomitant depression of the respiratory center is undesirable. An antihistaminic accomplishes this purpose well, and adds sedation. Since there is always a possibility that an allergic response plays a role in edema, some relief of the respiratory distress may occur. Steroids should be used to control inflammatory and allergic phenomena and swelling. If all this fails, and the patient is still restless and hypoxic, a tracheostomy should be performed immediately.

(concluded on following page)

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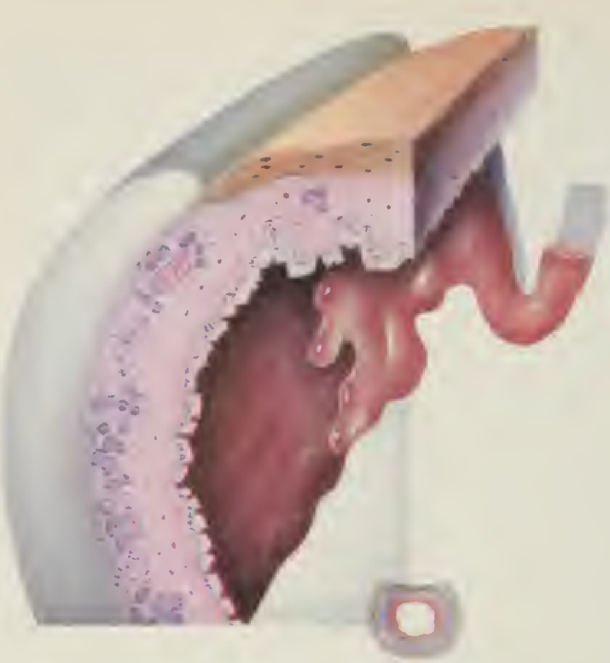

Cross section of trachea showing subglottic edema and lumen reduction due to mucous membrane congestion.

Pneumonia may also follow anesthesia administered to a patient with a cold. This can be caused by accumulated secretions becoming secondarily infected and causing consolidation of the lung. *Atelectasis* of the lung can result if one of the bronchioles becomes plugged by secretions, preventing aeration of the distal part of that lung. This is seen more frequently following upper respiratory infection because dry anesthetic gases aggravate the infection, causing secretions to change from watery to thick and viscid, and consequently difficult to suction.

Prevention of complications

The first rule to prevent complications, of course, is to use a regional or local anesthesia whenever possible. But when emergency surgery is a must, in spite of the presence of a cold, allergy, or upper respiratory infection, here are some ways to prevent complications.

Give nose drops preoperatively. This can help shrink the congested nasal mucous membranes and reduce secretions for better air passage. (Results of this method are sometimes unsatisfactory because of the short duration of effect or rebound congestion.) For longer effect, oral antihistamines with nasal decongestants are often given to provide and maintain a drying effect on secretions.

To clear the tracheobronchial tree, instruct the patient to cough preoperatively. Cold steam or water nebulizers effectively humidify the nasal, pharyngeal and bronchial passages and often make the patient more comfortable. Tenacious secretions become more watery under humidification, clear more thoroughly preoperatively and are more easily suctioned from the airway during anesthesia.

Give intravenous fluids to those patients who appear dehydrated due to a cold. In a well hydrated patient the respiratory tract secretions are less viscid and more watery. This is particularly true in asthmatics.

Summary:

Administration of emergency anesthesia to a patient with a cold or upper respiratory infection can lead to a chain of events that may result in increased postoperative morbidity and even death. This is because of the excess secretions formed in these conditions. Preoperative measures to prevent or reduce these secretions should be undertaken and will result in smoother and safer anesthesia.

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The Brain Drain in Medicine*

G. HALSEY HUNT, M.D., F.A.C.S.

Executive Director, Educational Council for Foreign Medical Graduates

It is a depressing and humbling experience for an American doctor to visit a medical school in one of the underindustrialized countries of Asia, to have his host open the conversation with a bland statement that "You people in the United States, and your hospitals, couldn't get along without our doctors," and to realize that at the present time this is indeed a fact. If the 11,000 foreign graduates who are now occupying internships and residencies in United States hospitals were to be suddenly withdrawn, many United States hospitals would be forced to curtail sharply their services to patients. I submit that for the long run this is a completely untenable situation. By almost any standard of measurement the United States is the richest country in the world. American standards of medical education and medical research and hospital practice are among the highest in the world. It ill becomes us to depend permanently on other countries for the production of medical manpower to provide services to American patients.

After their opening remarks about our needs for their doctors, foreign medical educators are likely to have some sharp comments about what we are doing to the other countries and their doctors. We are told that we are enticing substantial numbers of their doctors to come to the United States, many of whom never return (or at least do not return permanently) to their home countries, and that in any case we are not giving them the kind of training that fits them to come back to practice in their own countries.

Along with the complaints of the brain drain, however, our critics sometimes point out that we are draining the wrong people, and that our unorganized and hit-or-miss method of recruiting foreign graduates to come to United States hospitals for training sometimes attracts the poorer and less stable students. This may minimize the effect of the brain drain, to be sure, but some of the people with whom I have talked believe that it gives the United States a false impression of the caliber of medical graduates in other countries and the quality of the medical education they have had.

Goals for the Training of Foreign Medical Graduates

Looking far into the future, one hopes that American hospitals will eventually develop better ways of meeting their service needs than to depend on foreign medical graduates. At that time the United States can assume its rightful role in the training of foreign physicians, which I believe should have the specific design of training them to return home and to raise the standards of medical practice in their home countries, both by active participation in medical education and by exemplifying higher standards of personal medical practice.

Achievement of this goal will require a number of rather fundamental changes from our present ways of doing things. First, the selection of foreign physicians to come to this country for training should be related to the ability of the individuals and to their potential contribution to medical education and medical practice after they return home. Second, there should be a mechanism for assuring that the foreign physicians who are selected to come to the United States for training are placed in the training programs which will best meet their needs. Third, and possibly most important of all, clinical training programs in United States hospitals should be tailored to meet the needs of individuals who have come from other parts of the world with considerable variation in their educational backgrounds, and with a great deal of variation in the medical needs of their home countries. There is really not much point in training physicians to do open heart surgery or complicated brain surgery if they are going back to a country which is still struggling with problems of overpopulation, acute infectious diseases, malnutrition, and general lack of sanitation, unless the country itself desires and arranges for such highly specialized training.

Even before these ultimate goals are reached

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* Part of an address delivered at the Annual General Session of The Federation of State Medical Boards of the United States, in Chicago, February 8, 1966; reprinted by permission from the Federation Bulletin, 1966, 53, 98.

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there are a number of fields in which American hospitals and others concerned with the training of foreign medical graduates should be doing better for our foreign visitors. Some hospitals have done well in providing social and cultural opportunities for the foreign medical graduates on their staffs, but it appears that much more can and should be done. Here is a field in which hospitals should stimulate activities by, and utilize the services of, such organizations as the hospital auxiliary and the various community organizations which are already in existence for the benefit of visitors from other countries.

The Future of Hospital Services

It has become an article of faith in American medical and hospital circles that the best hospital practice is carried out in hospitals that have approved internship and residency training programs. Partly out of a desire to have the best possible hospital service, partly out of a desire to have interns and residents who can carry out some of the more routine activities of hospital and medical care, partly for reasons of prestige, and partly to meet the requirements of the Joint Commission on Accreditation of Hospitals with the least expenditure of time, money and effort, most voluntary hospitals which think they can meet the requirements of the AMA Council om Medical Education seek to establish at least an internship, and preferably one or more residency programs.

I think it can be demonstrated by some rather simple arithmetic that only a fraction of the general hospital patients in any country, the United States or any other, can be involved in what we consider a first-class internship. If we look upon the internship as a primarily educational experience, with service to patients an important but incidental matter, and if one accepts the standard that there should be no more than about 25 beds per intern in a proper program, it becomes rather obvious that a substantial proportion of general hospital beds cannot be utilized in first-class internship training as long as the internship is limited to the first year after medical school. As things stand at present only a fraction of all approved internship programs in the United States have the ideal ratio of interns to patients. In some of the others the interns (largely the foreign interns) are being used as hired hands to carry out the work of the hospital, with, we hope, some educational byproduct.

In my opinion, the only self-respecting position for American medicine and American hospitals to take in the long run is that the service needs of American patients should be met by American physicians. Such a state of affairs obviously cannot be achieved overnight, but I think it is the goal toward which we should work.

Some of the implications for American medical and hospital practice are rather obvious. If a large proportion of the "service work" in American hospitals is not to be done by interns in good training programs, or by foreign graduates who are acting as hired hands under the guise of internships, some other mechanism must be worked out to provide these services. There may be some alternative, but at the moment I can really think of no solution except the employment of licensed American physicians on a part-time or even in some cases on a full-time basis. This will require some readjustment of thinking and will cost the hospitals, that is, the American public, more than they are now spending for these services, though we hope they will get more for their money. As I said earlier, if stories of some of the salaries that are now being paid to foreign-trained "interns" are anywhere near accurate, the financial part of the problem may be gradually solving itself. In some places the salaries are already such that they might well attract young American physicians, at least for part-time work.

It is unlikely, however, that the problem will solve itself on a nationwide basis, and quietly go away. I suggest that American physicians, and American hospitals, and American medical educators and medical schools have a pressing present responsibility to develop ways and means of educating (and then properly utilizing) enough American doctors to meet the needs of the American people. We will then be in a position to select each year a substantial number of foreign physicians and train them properly, to establish a proper program of true international medical exchange.

Physicians Honored for Service in Vietnam

FIVE MEMBERS of the Medical Society of the District of Columbia were honored for their volunteer services to the people of Vietnam at a reception at the Vietnamese Embassy, Monday evening, June 20. They were: Drs. James D. Brew, Alan R. Crain, Robert L. Dow, Henry L. Feffer, and Fred A. J. Geier.

Briefly, the services rendered by these physicians were as follows: Dr. Brew was in Vietnam last January and February as gynecologist-in-charge of the Tu Du Hospital and Hung Vuong Hospital in Saigon. Dr. Crain performed orthopedic surgery at the Cho Ray Hospital in Saigon and also trained Vietnamese doctors in American techniques. Dr. Dow helped establish the first in- and outpatient clinics at Cho Ray Hospital during his 2 months there. Dr. Feffer organized the first orthopedic surgical training program in Saigon's Cho Ray Hospital. Dr. Geier was in charge of the Khoa Nghia Hospital in Can Tho last October and November. This hospital is located in the Mekong Delta, 70 miles southwest of Saigon.

His Excellency, the Ambassador Vu Van Thai of Vietnam and Dr. Robert J. Coffey, President of the D. C. Medical Society, who represented the American Medical Association, presented a Certificate for Meritorious Service to each doctor "in recognition of meritorious service performed for the people of South Vietnam, the United States Government and the medical profession during his voluntary medical mission." The certificates, supplied by the AMA, were presented at the request of the AMA and were signed by its President, Dr. James Z. Appel.

GUESTS OF HONOR at the Vietnamese Embassy, June 20, were 4 Washington physicians who volunteered their services to the civilians of Vietnam for 2 months each. Left to right are Dr. Alan R. Crain, Dr. Fred A. J. Geier, His Excellency, the Ambassador Vu Van Thai, President Coffey of the D. C. Medical Society, Dr. James D. Brew, and Dr. Henry L. Feffer. The doctors have just been presented certificates of appreciation from the Ambassador signed by the President of the American Medical Association. Dr. Coffey took part in the presentation as the official representative of the AMA.

The urgency of the need for doctors in Vietnam can best be emphasized by these facts: There are about 1,000 South Vietnamese doctors and approximately 70 per cent are in the military service. This leaves about 300 doctors to treat 15 million civilians in Vietnam.

One hundred and ten physicians have already served as volunteers; it is estimated that 32 are needed on a continuing basis to fill the needs of the program. A minimum of 60 days is the average tour of duty, and the AMA is now engaged in a stepped-up program to keep ahead of the turnover.

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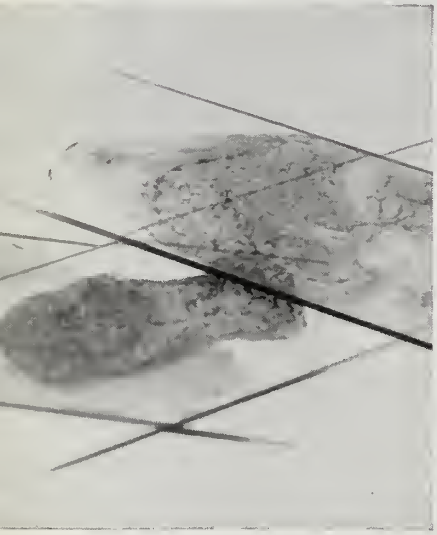

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Health Dept. Notes

Health Support in Head Start

Project Head Start, which began in the District on June 27, is an organized attempt to prepare disadvantaged children, ages 4, 5 and 6, for their first entry into school later in the year.

Some 7,000 youngsters may be enrolled in the Project, taking part in the combined learning and play activities. The Head Start Centers are located in 47 schools throughout the District and at 5 churches in the Cardozo area.

This is the second year for Head Start in D.C. and elsewhere in the country. It has been one of the more accepted programs related to the Federal poverty efforts and has generated considerable public interest and support.

The D.C. Department of Public Health has been providing the health screening and health services available to the Head Start Centers. During the 6 weeks of Head Start operation these services were scheduled so that all enrolled might benefit.

Each child in Head Start was able to participate in a physical examination by a physician, with findings and the history placed on the pupil's school health record. This was not required if a child was under medical care and had record of such an examination within the past 3 months. Each child received dental screening, and counseling and referral as appropriate. Vision and hearing tests were done on the youngsters, with counseling and referral as needed, and with an ENT evaluation on hearing failures made in the audiology clinic.

PPD tuberculin testing and readings on the children are carried out by registered nurses. Immunization against measles, a DPT booster, and a polio booster were given as needed. The DPT initial series was begun at Head Start and continued at regular immunization clinics. Smallpox protection was also available at Head Start. Urinalysis and blood hemoglobin tests were done for each child, with the physician taking blood at the time of examination. Urine testing was performed by the nurse in the Head Start Centers.

Mental health consultation was offered to the Head Start staff to aid in detecting behavior and learning problems or more severe problems if existing. Counseling was also provided to parents individually and in groups.

Information relating to food and nutrition was offered to Head Start teachers and staff and to families of the children enrolled, with direct consultation to those children and families who might benefit from this.

Accident prevention in the home was featured for both families and the children, with emphasis on poison prevention through education and instruction. Good health practices, family living, and other topics of health education were provided for Head Start staff, the youngsters and their parents, using films, illustrated pamphlets and a 30-minute puppet show presentation.

This sampling of health services indicates how wide a range of activity can be encompassed in an organized applied health effort.

The 52 Head Start locations required tight scheduling of tests and services throughout the 6-week session. There was necessarily some interchangeability of medical and nursing staff and the need to be organized without creating a locked-in rigidity.

Some readers of this journal may have taken part in a phase of the District's Head Start Project this summer, perhaps in the physical examination of the children or in their immunization. Through these efforts 7,000 boys and girls in Washington will enter school this fall with some assurance that their health problems have been taken care of.

Murray Grant, M.D., D.P.H.
D. C. Director of Public Health

First Evaluation of Uterine Cancer Project

Twenty-five per cent more PAP smears have been received by 21 laboratories in the Washington Metropolitan Area the first quarter of this year as compared to the same period last year, according to the first evaluation report of the Washington Metropolitan Area Uterine Cancer Project Committee. This report has just been released by the American Cancer Society, which has been conducting a public and professional education campaign on uterine cancer since January 1, 1966.

One hundred and forty-eight physicians in the Washington Metropolitan Area reported a 38 per cent increase in pelvic examinations, including a PAP test, in the same period. A number of physicians reported greater interest in having the PAP test done as a result of the area-wide publicity on conquering uterine cancer.

Heart Association Elects New Officers

Memorial Exhibit to Dr. Lee

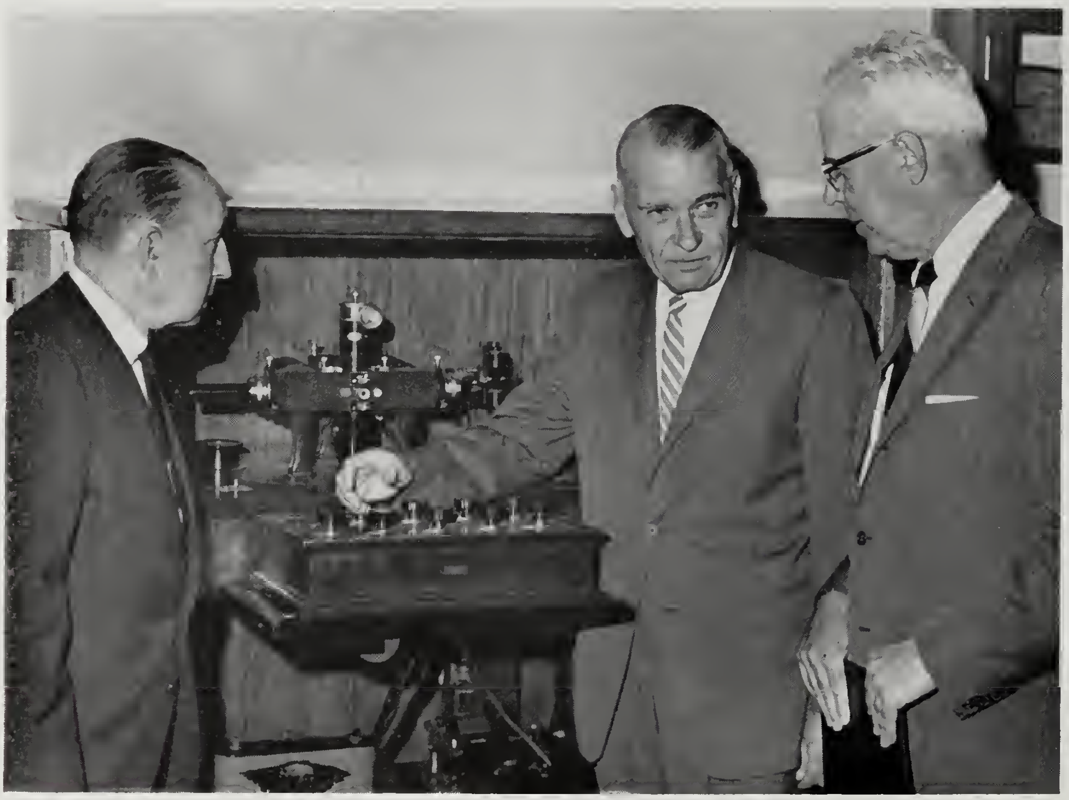
Dr. Jack Kleh was elected President of the Washington Heart Association at its Annual Meeting, June 21, in the D. C. Medical Society's building. A native Washingtonian, Dr. Kleh is Associate Clinical Professor of Medicine at George Washington University School of Medicine, Associate in Medicine and Chairman of the Section on Geriatrics, George Washington University Hospital, and Medical Director of the D. C. Department of Public Welfare. He succeeds Dr. John F. Finnegan as President of the Association.

Dr. Charles A. Hufnagel is the new President-elect. Dr. John M. Evans was elected Vice President; Dr. John B. Johnson, Secretary; Mr. John E. Sumter, Treasurer; and Mr. Kenneth Birgfeld, Assistant Treasurer.

A special feature of this meeting was the showing of an electrocardiograph machine as a memorial exhibit to the late Dr. Thomas S. Lee, founder and first President of the Washington Heart Association. This electrocardiograph, the first used by a Washington physician in his office, was purchased by Dr. Lee in 1924. Now the property of the Smithsonian Institution, it was loaned for this exhibit and will remain on view in the Exhibit Hall of the D. C. Medical Society building for 1 year.

In reporting on the activities of the Washington Heart Association during his year in office, Dr. Finnegan stressed the fact that the program of the Heart Association is made possible with funds raised through the Heart Fund campaign, which in 1966 was by far the largest amount ever raised, over $440,000; nearly one-half of this came from the Federal Government employees through the Combined Federal Campaign. A special achievement of the Women's Board this year was the support of an American Heart Association Teaching Scholarship, which was recently awarded to Dr. T. James Waters, of Georgetown University.

An award for special service to the Association was presented to Dr. Finnegan, retiring President.



MEMORIAL EXHIBIT TO DR. THOMAS S. LEE: Dr. John A. Reisinger (center), head of the Lee Memorial Committee, explains the operation of the electrocardiograph machine, first used in Washington by Dr. Lee, to Dr. Robert J. Coffey (right), President of the D. C. Medical Society, and to Dr. John F. Finnegan, retiring President of the Washington Heart Association. The instrument, on loan from The Smithsonian Institution, will be on display in the Medical Society's building for a year.

Dr. Kleh, who assumed the presidency of the Heart Association, July 1

Drs. John A. Reisinger, Thomas W. Mattingly, and Benjamin Manchester were also cited for special service and were elected to honorary membership on the Board of Directors.

New members elected to the Board for 2-year terms included Drs. James M. Bacos, Lewis Gillespie, Jr., Edward W. Hawthorne, Frank I. Marcus, Alvin E. Parrish, Gerald I. Shugoll, and Stanley M. Silverberg. Among those reëlected to 2-year terms were Drs. Evans, Finnegan, Hufnagel, Kleh, Clayton B. Ethridge, William L. Howell, George A. Kelser, John W. Latimer, Frank G. MacMurray, Andrew G. Prandoni, Estelle R. Ramey, George E. Schreiner, and Bernard J. Walsh.

Congress on Medical Quackery

THE THIRD NATIONAL CONGRESS on Medical Quackery will be held at the Pick-Congress Hotel in Chicago, October 7 and 8, 1966.

The American Medical Association and the National Health Council, the Nation's largest organizations of professional, governmental and voluntary agencies in the health field, will serve as co-sponsors of the October Congress. The 2 previous National Congresses on Medical Quackery, in 1961 and 1963, were held in Washington, D. C.

The October Congress will be based on the theme, "Quackery: 1966" and will be aimed at calling to the attention of the Nation the perils posed by present-day fads and fallacies in the health field.

Details of the Congress, including the program of nationally recognized speakers, will be announced in the near future. Inquiries should be addressed to John G. Thomsen, M.D., Chairman, American Medical Association, Committee on Quackery, 535 North Dearborn Street, Chicago, Ill. 60610.

Joint Committee on Health Problems in Education

THE FOLLOWING RESOLUTIONS, briefly stated, were adopted by the Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association at its Annual Meeting in Washington, D. C. on February 27, 28, and March 1, 1966.

Legislative Guidelines and Regulations: That it become the general practice of governmental groups developing guidelines which significantly affect local policies and practices to seek the counsel of the professional personnel who are to carry out the programs involved, to permit optimum local adaptation and innovation, and insure that those guidelines that are developed be as flexible as is consistent with good administrative practice.

Governmental Promotion of Smoking: That Federal, State, and local governmental agencies refrain from supporting or distributing propaganda which might tend to encourage young people to initiate the undesirable practice of smoking.

School Health Legislation: That future legislation utilize to a greater degree practicing, experienced, professionally trained medical and educational leaders and organizations to assist in the drafting of legislation; that schools be encouraged to include health services and health education in their new experimental and innovative educational programs; and that future legislation should emphasize health in the schools to the same degree that other subjects are supported and emphasized.

Undue Pressures on Educators: That boards of education provide healthful working conditions for school administrators and classroom teachers; that boards of education establish policies to lighten teacher load and class size, such as the use of teacher aides; and that educators be granted time each day to carry out nonteaching functions, prepare instructional plans, and to relieve excessive stress.

Need for Control in Educational Research: That funds for research in child development be sought to support a carefully planned study to evaluate new techniques in teaching reading, and that until the results of such scientifically controlled research are available, it is suggested that education and health agencies not adopt unproven methods of teaching reading.

The Joint Committee on Health Problems in Education of the NEA and the AMA has been in

(Continued on page 456)

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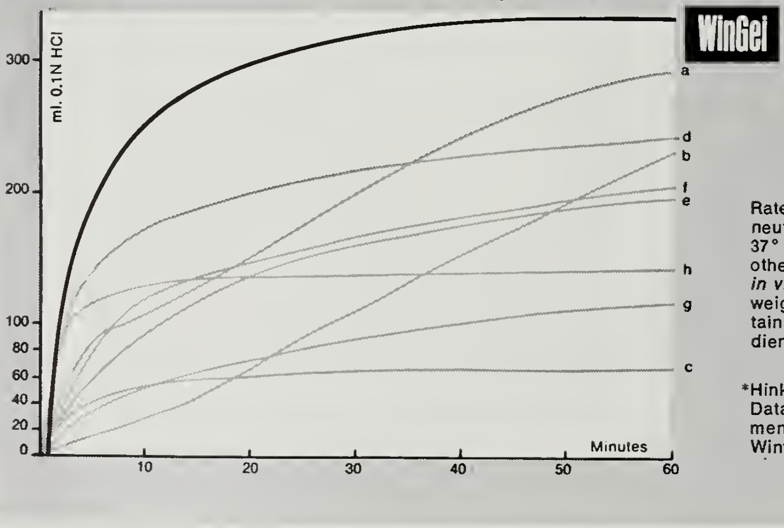
New WinGel neutralizes 300 times its active-ingredient weight in 0.1N hydrochloric acid—neutralizes more acid faster than other leading antacids



Rate of 0.1N hydrochloric acid neutralization at pH 3.5 and 37° with WinGel and eight other leading antacid tablets—*in vitro*. Samples equaled the weight of tablet material containing 1.0 Gm. active ingredients.*

*Hinkel, E. T., Jr. (New York): Data in the files of the Department of Medical Research, Winthrop Laboratories.

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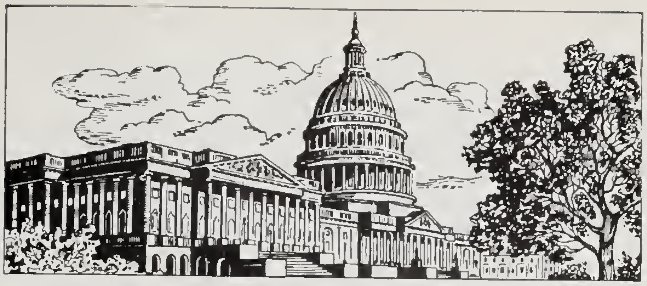

NEWS & PERSONALS

Meetings

The Communicable Disease Center of the Public Health Service, Atlanta, Ga., is sponsoring 4 **C.D.C. Seminar Services** in Washington, all of them scheduled at the new Headquarters building of the D. C. Medical Society. The first, on the subject of Salmonellosis, was held, June 23. Two will be held during the fall months, and the last, early in 1967.

Dates and topics are as follows:

September 22: **Immunization.** This seminar will be concerned with polio, measles, rabies, smallpox vaccines, efficacy of immunizing agents, and precautions and complications of immunizing agents.

October 20: **Viral Hepatitis.** Clinical management and diagnosis will be discussed, as well as the etiology of this disease. Other topics will include the epidemiology of viral hepatitis and the use and abuse of gamma globulin.

February 16, 1967: **Tuberculosis.** All aspects of this disease will be presented, including chemotherapy, drug resistance, epidemiology, re-treatment regimens, chemoprophylaxis, tuberculin testing, and air-borne infections.

The III International Congress of Nephrology will be held in the Washington Hilton Hotel, Washington, September 25–30, 1966. Dr. Robert W. Berliner, of the National Institutes of Health, is President of the Congress; Dr. George E. Schreiner, Professor of Medicine at Georgetown University, is Secretary General.

Participation in the Congress is open to scientists and physicians throughout the world who are interested in problems relating to the kidney. Membership in the Congress may be obtained through payment of the active member registration fee; membership in the sponsoring or cooperating organizations is not a prerequisite to membership in the Congress.

Inquiries may be addressed to: Secretariat, III International Congress of Nephrology, 9650 Wisconsin Avenue, Washington, D. C. 20014.

General News

Dr. Charles Mayo Goss, who has 4 times edited "Gray's Anatomy of the Human Body," the "anatomic bible," has been **appointed to the faculty of George Washington University School of Medicine** as Visiting Professor of Anatomy. The appointment became effective, July 1.

Dr. Goss has researched and written in the fields of experimental embryology, especially the earliest development of the heart in living mammalian embryos. However, he is not only a scientist and editor of medical texts but a classical scholar. He has published translations of 4 of Galen's anatomical treatises from Greek and is an authority on the history of medicine in ancient Greece.

Professor of Anatomy at Louisiana State University since 1947, Dr. Goss served previously on the medical faculties of the Universities of Alabama, Columbia, and Yale, where he received both his undergraduate and medical degrees.

The First Annual Dr. Maynard I. Cohen Memorial Award was shared by 2 young women pediatricians at graduation ceremonies for residents and fellows, June 20, at Children's Hospital. The recipients were Dr. Abigail Farber, of Bethesda, Md., and Dr. Karen N. Olness, of Washington. These Assistant Chief Pediatric Residents were honored for "intense interest, diligence and excellence of judgment in the care of the pediatric patient." Dr. John A. Washington, Chairman of the House Staff Education Committee, presented the citations, which include a monetary award.

The late Dr. Cohen, of Chevy Chase, Md., died in 1961. He was elected an Active member of the D. C. Medical Society in 1947 and transferred to Associate membership in 1952. His family has established this award in his memory.

Dr. Camalier, new head of Medical Service

Dr. C. Willard Camalier, Jr., Washington surgeon, has been elected **President of Medical Service of D. C.,** succeeding Dr. Henry L. Darner, who had served in that capacity since 1961. Other officers elected at the June meeting of the Board of Directors were Dr. Leonard T. Peterson, First Vice President, and Dr. John S. Haught, Second Vice President. Mr. George B. McGovern, Executive Vice President, was reelected Secretary and Mr. Douglas R. Smith, President of the National Savings and Trust Company, was reëlected Treasurer. Two new trustees were elected to the Board, Dr. Edward W. Nicklas and Dr. Charles E. Bickham, Jr., succeeding Dr. Darner and Dr. Alfred A. J. Den, respectively.

Dr. Camalier received his medical degree from Duke University School of Medicine in 1938. Except for 3 years of service in the Army, much of which was in the European Theater of Operations, he has engaged in the private practice of surgery since 1942. He served as Chairman of the Committee on Medical Care of the Medical Society of the District of Columbia from 1954 to 1959 and is the Medical Society's junior delegate to the American Medical Association. He is senior attending surgeon at the Washington Hospital Center and Sibley Memorial Hospital.

The National Heart Institute has prepared a new leaflet, **"Emphysema"** (PHS Publication No. 1414), single copies of which may be obtained free from the Public Health Service, Department of Health, Education and Welfare, Washington, D.C. 20201.

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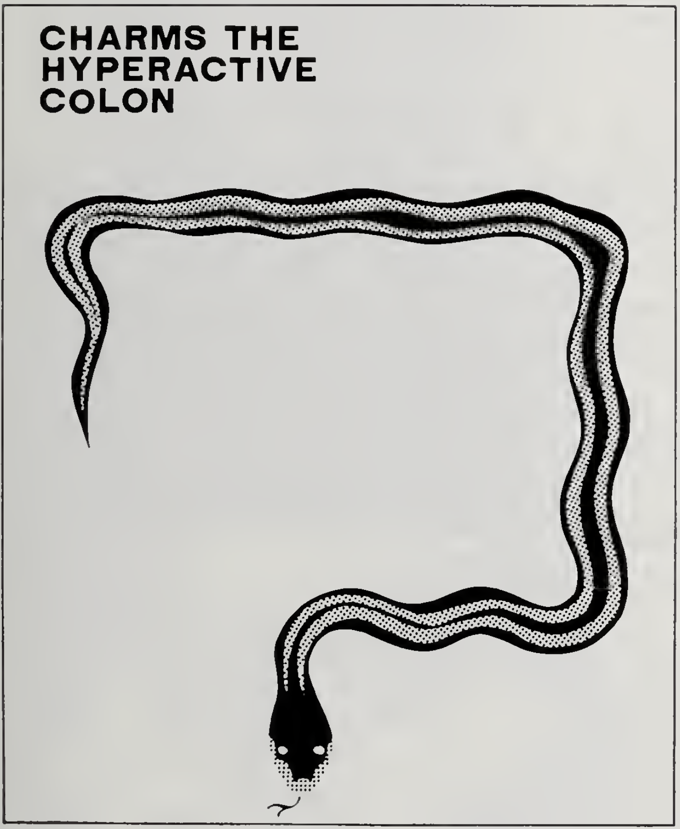

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The leaflet describes the symptoms and treatment of emphysema. The causes of emphysema are still unknown but certain factors are suspect. Exposure to lung irritants, disease-producing organisms, polluted air, cigarette smoke, and allergic materials are thought to contribute to the development of emphysema. It is estimated that from 1 to 10 million Americans are afflicted to some degree by this disease. It is more widespread than lung cancer and tuberculosis combined, and almost as prevalent as arthritis.

Mr. William Becque, Executive Director of the D. C. Tuberculosis Association for the past 8 years, has accepted the position of **Executive Secretary of the National Tuberculosis Association.**

The fourth E. K. Funkhouser Memorial Award for distinguished service in public health was presented to Mr. Becque at the 64th Annual Meeting of the Association, May 2, at the National Press Club.

The District of Columbia Dental Society, at its meeting, June 14, elected new officers for 1966-67. They are:

Dr. Balfour D. Mattox, *President*; Dr. Anthony P. Culotta, *Vice President*; Dr. James J. Connors, *Secretary*; and Dr. Joseph R. Salcetti, *Treasurer*.

Personals

Dr. Roy Hertz has been appointed Professor of Obstetrics and Gynecology at the George Washington University School of Medicine, effective July 1. He comes to George Washington from the National Institutes of Health, where he was Chief of the Endocrinology Branch of the National Cancer Institute from 1948 to 1965 and since then has served as Scientific Director of the National Institute of Child Health and Human Development. He is a graduate of the University of Wisconsin School of Medicine, Class of 1939, and received the degree, Master of Public Health, from Johns Hopkins University in 1941.

Dr. Herbert S. Gates, Sr., received the 1966 Sibley Medical Association Achievement Award at the Tenth Annual Meeting of the Association, May 5. He was presented with an engraved silver tray by Dr. Thomas F. Cullen, President of the Association.

Dr. Brian Blades has resigned as a national consultant in thoracic surgery to the Veterans Administration after serving for more than 20 years in that post. In a special ceremony, Tuesday morning, June 14, he received a Certificate of Commendation from Dr. H. Martin Engle, Chief Medical Director, at the new VA Hospital on Irving Street. Present were the VA Board of Surgical Consultants, of which Dr. Blades has been a member for many years.

DR. BRIAN BLADES expresses his appreciation for the certificate of commendation which he has just been awarded by Medical Director Engle for his 20 years of service as a national consultant in thoracic surgery to the Veterans Administration.

A member of the original committee advising the VA in surgery, Dr. Blades initiated and has developed national, regional and local programs and personnel in the field of surgery for VA, and he has served on numerous advisory groups for programs in the 165 VA hospitals.

Dr. Fritz A. Freyhan has accepted an appointment as Director of Research and Attending Psychiatrist in the Department of Psychiatry at St. Vincent's Hospital and Medical Center of New York. Dr. Freyhan has been Deputy Chief in Charge of Clinical Studies at the Clinical Neuropharmacology Research Center at the National Institute of Mental Health, and will remain on leave of absence from the Institute until the end of the year. He has transferred his private practice of psychiatry from Washington to 11 Riverside Drive, New York, N.Y. 10023.

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Pancreatin 3X** (source of lipolytic activity), 100 mg.; Taurocholic acid, 15 mg.

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**As acid resistant granules equivalent in activity to 300 mg. Pancreatin N.F.

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Dr. James J. Feffer is the new President-elect of the American Society of Internal Medicine.

A student prize in honor of **Dr. Benjamin Manchester** has been established at George Washington University School of Medicine through an endowment by a grateful patient. The prize will be given annually to a member of the graduating class "who has been not only outstanding in his or her work but who also shows promise of real humanitarianism in the practice of medicine."

Dr. Thomas M. Peery, Chief of the Department of Pathology, George Washington University School of Medicine, was awarded an honorary degree in medical science, May 29, by his alma mater, Newberry College, at Newberry, S. C. Dr. Peery received his undergraduate degree from Newberry in 1928.

Dr. David H. Kushner was chairman of a section which participated in the scientific program of the Fifth World Congress on Fertility and Sterility, held in Stockholm, Sweden, June 16–22. He also presented a paper, "Diagnosis of Carcinoma of Cervix Uteri in Pregnancy" from Columbia Hospital for Women, Washington, D. C. which was co-authored with T. R. Turner, Dr. W. J. Jaffurs, and Dr. J. E. Medina. The Sixth World Congress will be held in Israel in 1968.

Dr. Bartolo M. Barone, Clinical Instructor in Neurosurgery at Georgetown University School of Medicine, was inducted into the Medical Corps of the United States Navy on August 1 and will serve as a neurosurgeon at the Naval Hospital in Charleston, S. C. for a 2-year period. Dr. Barone was recently elected to Associate membership in the D. C. Medical Society.

Benefit for Nurses and Medical Students at Italian Embassy

His Excellency, the Ambassador of Italy and Signora Fenoaltea were host and hostess to members and guests of the Woman's Auxiliary to the Medical Society of the District of Columbia at a reception, May 14, from 6 to 8 p.m. The occasion was a benefit to raise money for nursing scholarships and for the AMA-ERF fund. About 200 persons were present to enjoy the generous hospitality of the Ambassador.

At the head of the receiving line was Mrs. O. Hugh Fulcher, President of the Woman's Auxiliary, who introduced each guest to the Ambassador and Signora Fenoaltea. Also in the receiving line were Dr. Robert J. Coffey, President of the Medical Society, and Mrs. Coffey; Mrs. Thomas N. Carter, President-elect of the Auxiliary, and Dr. Carter; and Dr. Fulcher. Chamber music by Devron Orchestra added to the enjoyment of the food and beverages served from a bountiful buffet. During the festivities Dr. Coffey presented an award of appreciation to the Ambassador in behalf of the Woman's Auxiliary. Past Presidents of the Auxiliary were hostesses and teenage daughters of members served as junior hostesses.

Mrs. Alfred J. Suraci chairmaned the benefit. The Auxiliary acknowledges its debt to Peoples Drug Stores for printing the invitations and to the many business establishments which contributed advertising space in the program. More than $2,500 was realized from the affair and will be used for nursing and medical student scholarships.

For cold hands and feet, nothing beats hot stoves—but they *are* awkward to carry around. Now Gerilid, in good-tasting take-along chewable tablets can provide rapid vasodilation of peripheral circulation, bringing real warmth to the extremities and decreasing sensitivity to sudden temperature change. Patients *like* Gerilid and *know* they are getting relief.

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(*Continued from page 413*)

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Medical Education and the Community—Stewart

(*Continued from page 417*)

Will you recognize your patients as surely as you recognize their diseases?

Will you level with them or lie to them, and what circumstances will determine which?

How will you perform when called upon in an emergency situation anywhere without supporting services?

How will you behave when you simply don't know the answer?

How will you behave when medical science doesn't know the answer, or when the only answer involves extreme risk?

Are you solidly sure of your motivations, especially in terms of money versus care?

Will you take the trouble to remember that your patient is a human being? What is a human being, anyway? What does he need that you can give him?

Your generation of physicians can build a bridge back to the needs of people and carry the wealth of scientific knowledge across it. That is the only way we can meet the crisis of unfulfilled expectation that confronts us.

Traumatic Thrombosis of Femoral Artery—Keshishian

(*Continued from page 422*)

struction not been attempted. Even so, this was risky, since the traumatized area had a good deal of detritus in the wound, i.e., dirt, gravel, cinder, and pieces of clothing. It has been recognized that autogenous venous grafts will tolerate implantation in a potentially infected site far more readily than dacron or other vascular prostheses. This is primarily because autogenous tissue is more readily acceptable and does not lead to a rejection phenomenon as often.^{3} Interrupted sutures were used for the anastomosis to permit growth of the anastomotic line. As others have shown, if anastomoses are made with continuous running sutures of nonabsorbable material, growth there is not possible. In repairing coarctation of the aorta in children it is common practice to interrupt the anterior layer of sutures. In the present case all sutures were placed in interrupted fashion not only to allow for growth but for technical ease. Since a 24-month period has elapsed with patency of the graft, I feel confident that it will continue to remain patent. The patient is being examined every 6 months.

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A-V Block Induced by Respiration—Khan et al

(*Continued from page 425*)

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Health Problems in Education

(*Continued from page 447*)

continuous existence since 1911, the oldest joint venture of either parent organization. Each organization selects 5 members for the Joint Committee, representing as wide a diversity in specialties as possible. The Committee's primary purpose, as stated in the minutes of the Annual Meeting in February 1939, has been: "To consider principles and policies affecting the health of children and youth which are the mutual concern of the 2 professions."

Dr. Harold M. Hobart, of Washington, is Vice Chairman of this Committee.

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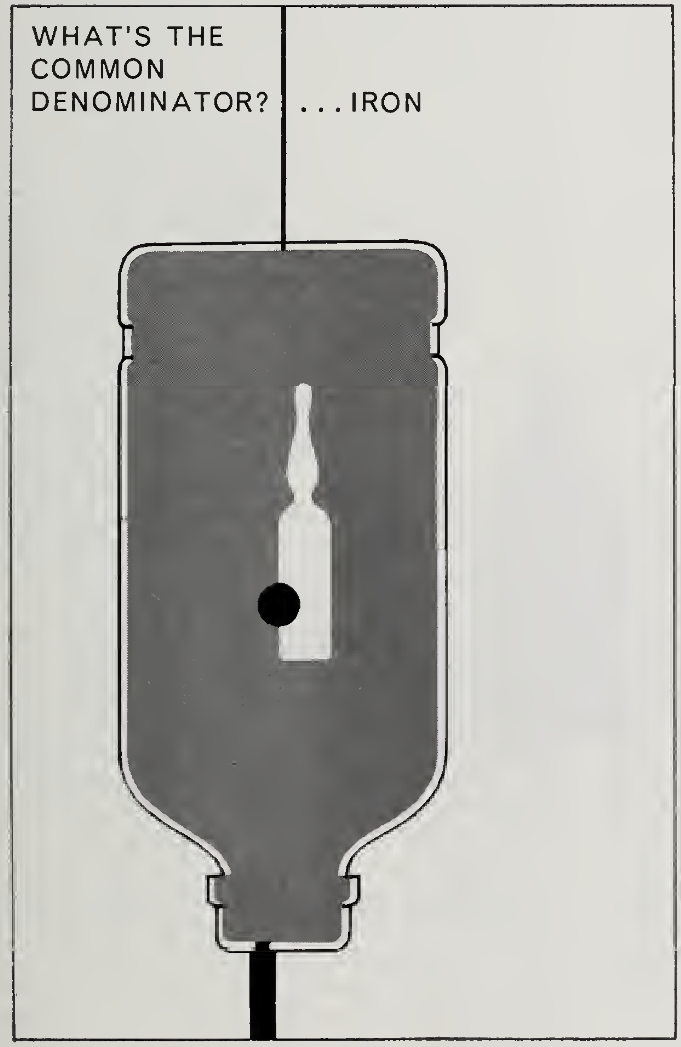

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IN BRIEF: ACTION AND USES: A single dose of Imferon (iron dextran injection) will measurably begin to raise hemoglobin and a complete course of therapy will effectively rebuild iron reserves. The drug is indicated only for specifically-diagnosed cases of iron deficiency anemia and then only when oral administration of iron is ineffective or impractical. Such iron deficiency may include: patients in the last trimester of pregnancy; patients with gastrointestinal disease or those recovering from gastrointestinal surgery; patients with chronic bleeding with continual and extensive iron losses not rapidly replenishable with oral iron; patients intolerant of blood transfusion as a source of iron; infants with hypochromic anemia; patients who cannot be relied upon to take oral iron.
COMPOSITION: Imferon (iron dextran injection) is a well-tolerated solution of iron dextran complex providing an equivalent of 50 mg. in each cc. The solution contains 0.9% sodium chloride and has a pH of 5.2-6.0. The 10 cc. vial contains 0.5% phenol as a preservative.
ADMINISTRATION AND DOSAGE: Dosage, based upon body weight and Gm. Hb/100 cc. of blood, ranges from 0.5 cc. in infants to 5.0 cc. in adults, daily, every other day, or weekly. Initial test doses are advisable. The total iron requirement for the individual patient is readily obtainable from the dosage chart in the package insert. Deep intramuscular injection in the upper outer quadrant of the buttock, using a Z-track technique, (with displacement of the skin laterally prior to injection), insures absorption and will help avoid staining of the skin. A 2-inch needle is recommended for the adult of average size.
SIDE EFFECTS: Local and systemic side effects are few. Staining of the skin may occur. Excessive dosage, beyond the calculated need, may cause hemosiderosis. Although allergic or anaphylatoid reactions are not common, occasional severe reactions have been observed, including three fatal reactions which may have been due to Imferon (iron dextran injection). Urticaria, arthralgia, lymphadenopathy, nausea, headache and fever have occasionally been reported.
PRECAUTIONS: If sensitivity to test doses is manifested, the drug should not be given. Imferon (iron dextran injection) must be administered by deep intramuscular injection only. Inject only in the upper outer quadrant of the buttock, not in the arm or other exposed area.
CONTRAINDICATIONS: Imferon (iron dextran injection) is contraindicated in patients sensitive to iron dextran complex. Since its use is intended for the treatment of iron deficiency anemia only it is contraindicated in other anemias.
CARCINOGENICITY POTENTIAL: Using relatively massive doses. Imferon (iron dextran injection) has been shown to produce sarcoma in rats, mice and rabbits and possibly in hamsters, but not in guinea pigs. The risk of carcinogenesis, if any in man, following recommended therapy with Imferon (iron dextran injection) appears to be extremely small.
SUPPLIED: 2 cc. ampuls, boxes of 10; 5 cc. ampuls, boxes of 4; 10 cc. multiple dose vials.

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BOOK REVIEWS

An Atlas of Fine Structure. The Cell. Its Organelles and Inclusions. Don W. Fawcett, M.D. Price, $11.00. Pp. 448, with 240 figures. Philadelphia: Saunders, 1966.

This book is essentially an atlas picturing the detailed internal structure of the cell. The work is based upon a series of original electron micrographs selected to aid in mapping the sites of cellular function. The pictures were originally prepared for use as a loan set for students at Harvard Medical School.

It is a fascinating book, equally pleasing for its concise, clearly-worded text and for its well-chosen, remarkably sharp, full-page pictures. One who has studied cells only through the light microscope will have some difficulty in recognizing his old friends here. Furthermore, he will encounter a whole new vocabulary, since names must be given to the new structures that are revealed when cells are studied at 100 times the magnification available with light microscopy. The time and effort spent in learning this new approach are certainly rewarded, however, since one gains a much clearer understanding of how cells function.

No attempt is made in this book to characterize the various cell types as such; thus liver cells are not considered in any systematic fashion. Instead the author has focused on each of the submicroscopic cell components, such as mitochondria, lysosomes and cell inclusions, and has compared these components as they are seen in various cell types and various species, emphasizing the similarities and the differences under different circumstances. Dr. Fawcett has noted that 3 widely different cell types, all characterized by motility, have a remarkably similar apparatus to achieve this motion. The flagella of certain Protozoa, the cilia of certain epithelial cells, and the tails of spermatozoa of many animal species all have a bundle of 11 long internal fibrils, 2 of which are centrally placed and 9 of which are evenly spaced about the center, appearing in cross section like the numbers on the face of a clock. While the functional significance of such details is not always understood, certain molecular fingerprints can often be identified.

As the author says in his foreword, it is very likely that one who reads critically the medical literature of tomorrow will need to understand the subcellular basis of organ function, as revealed in this handsome collection of electron micrographs.

Thomas M. Peery, M.D.

Fifth National Cancer Conference Proceedings. Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, September 17, 18 and 19, 1964. Sponsored by American Cancer Society, Inc. and National Cancer Institute. Pp. 764, illustrated. Philadelphia: Lippincott, 1965.

The Proceedings of the Fifth National Cancer Conference of 1964 is a 700-page reference book on cancer which should be in every practitioner's library. It is also a monument to the prodigious efforts of the Program Committee, its Chairman, Dr. Roger H. Harvey, and to the American Cancer Society and its tireless efforts in combating cancer.

The first 100 pages of the book deal with the Epidemiology and the biology of cancer and is recommended reading material for all workers in the field of cancer. The chapters on Viruses as Related to Cancer, Role of Immunity in the Biology of Cancer, and Biologic Aspects of Cancer Cell Spread are classic presentations and offer an amazing insight into the problems involved in the prevention and cure of human cancer.

The remainder of the book deals largely with the clinical aspects of cancer and current methods of cancer control. In the section dealing with breast cancer the new techniques of mammography and thermography, useful in the early diagnosis of breast cancer, are discussed. There are no new additions in the chapter dealing with hormone therapy and adjuvant chemotherapy in the management of breast cancer. That portion of the book dealing with cancer of the cervix reëmphasizes the role of the Papanicolaou smear test in improving cancer survival statistics and indicates the importance in the proper selection of patients for surgery and/or radiation therapy. In the section on oral and laryngopharyngeal cancer the indications for the selection of patients for irradiation and for surgical treatment and the end results of the methods of treatment are presented. It is of great interest to note that the section dealing with cancer of the prostate and urinary bladder indicates no substantial improvement in the survival rate during 1955 to 1959 for both prostatic and bladder cancer. Likewise, the end results of the study on cancer of the bone revealed a higher 5-year survival for females which is not readily explained.

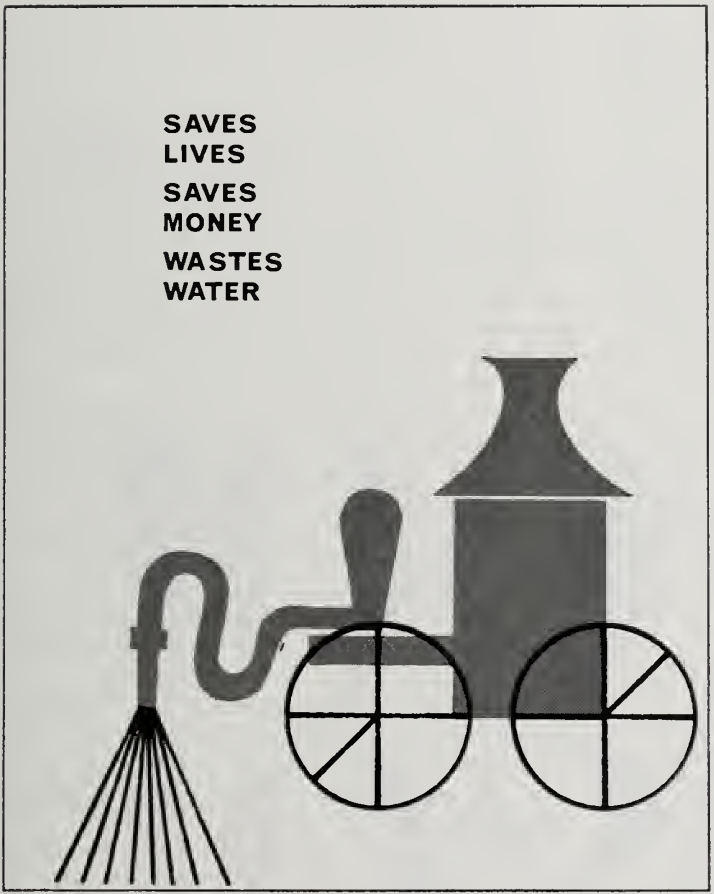
In the section dealing with Cancer and the Patient some insight is given into the problem of protein metabolism and how it undergoes certain alterations in the patient suffering from cancer. The one philosophical chapter in the book deals with the future role of preoperative irradiation in the treatment of cancer of the breast, lung, bladder, head and neck, and rectum. Some of the statements in this chapter seem on the surface far-fetched.

Radiation therapy has been employed in many different ways in the treatment of cancer for a great many years. The end results have not been particularly rewarding. To believe that a new application of preoperative irradiation is going to cure many forms of cancer is wishful thinking.

Included in the book is an extensive presentation of current knowledge regarding perfusion of melanoma and chemotherapy in other tumors of different anatomical sites. The chapters on malignancies of the colon, rectum and on leukemia and lymphomas appear adequate.

The last chapter in the book covers the trends in cancer therapy and patient survival for the past 20 years. For the 20-year period from 1940 to 1959 there were 2 major trends noted: (1) increased use of surgery in the treatment of solid tumors, and (2) a sharp in-

(Continued on page 42)



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Book Reviews

(*Continued from page 40*)

crease in the use of chemotherapy in the management of the lymphomas and the leukemias. Survival rates for various forms of cancer increased during this period; however, the upward trend of survival rates for patients with solid tumors appears to be leveling off.

The book is an encylopedic reservoir of current knowledge concerning most of the aspects of cancer as we see it today. It is recommended reading for all scientists and practitioners interested in cancer.

J. KEITH CROMER, M.D.

Ciba Foundation Symposium: Transcultural Psychiatry. Edited by A. V. S. DEREUCK, M.Sc., D.I.C., A.R.C.S., AND RUTH PORTER, M.R.C.P. Price, $12.00. Pp. 396, with 10 illustrations. Boston: Little, 1965.

There are presented in this edition of Ciba's first psychiatric symposium the papers and discussions of 24 psychiatrists, anthropologists, psychologists, and epidemiologists, including Washington's W. Caudill. Brought together are not only representatives of several disciplines but also of several cultures. As a result there is a tendency to emphasize exotic cultural contrasts rather than theoretic implications.

The Symposium opens with an introduction to recent developments in the field together with a survey of the literature. A paper on the origin of culture from prehuman precursors in terms of social organization presents an anthropologic view of the internalization of experience with speculations on the development of psychic structure.

A section on cross-cultural variations in psychiatric symptomatology includes presentations on schizophrenia in primitive and modern Africa, on affect disorders in Chinese cultures, and on the influence of housing on mental health in Israel. Provocative comments raise questions relevant to our Western theory and therapy, comments on such matters as the mildness of guilt and shame in depressed Chinese, and the rarity of delusions of grandeur in paranoid primitive Africans. Some of the genetic implications are considered.

There follows a discussion of cultural variations in the care of the ill, including social aspects of ideas about treatment. A paper by Carstairs of Edinburgh on cultural elements in the response to treatment is one of the highlights of the book. The role of suggestion and its relationship to magic, fantasy and myth is extremely relevant not only to the various psychotherapies but to all of medicine.

In the section on the interaction of social factors in mental health, there are papers on changing patterns of adolescence, psychiatric disorder, and adult roles. Worthy of note, especially to pediatricians, is a paper by Wolfenstein in which modern adolescence is reviewed in the light of 2 recent trends: the starting of a new family before material independence has been attained and the initiation of sexual realtionships before the emergence of tender romantic feelings. The final section presents further detail on problems of methodology on transcultural research.

As with so many symposia, the transcribed discussions are much more lively and stimulating than the papers they follow. Although, fortunately, not a handbook of yet another new subspecialty, this volume is fascinating in its variety, providing unexpected perspectives on questions at the frontiers of Western psychologic theory.

WARREN S. POLAND, M.D.

Man and Africa. A Ciba Foundation Symposium, jointly with The Haile Selassie I Prize Trust under the patronage of His Imperial Majesty Haile Selassie I, Emperor of Ethiopia. Edited by GORDON WOLSTENHOLME AND MAEVE O'CONNOR. Price, $7.50. Pp. 400, with 24 illustrations. Boston: Little, 1966.

This book will interest physicians planning a visit to Africa, and it would be very helpful to doctors and public health workers who plan to work there or in any undeveloped country, not so much for its medical and public health viewpoints as for the comprehensive view of the country's problems and potentials. Although some of the problems explored also face the "developed" countries, the general medical reader will prefer to study developments closer to home.

This is the report of a Ciba Foundation Symposium held in Addis Ababa in October 1964. Each of 16 experts from Africa, Europe, Asia, and the United States presented his views on one o the problems facing the developing nations and the continent of Africa. Each presentation was followed by discussion, which is reported verbatim. Problem areas ranged from multiplicity of tribal languages, through development of water supplies, to effects on mental health of socioeconomic changes.

Readers will note that there are some 125 political units on the globe, and at the moment Africa claims more than 50 of them. Although it is the second largest continent, with 25 per cent of the land surface and 8 per cent of the world's population, it contributes only 2 per cent of the total value of world output. The country as a whole is underpopulated. There is 1 doctor for about 20,000 people. However, with the spread of medical service the population is expected to double in the next 30 years.

The book brings out the effects of medicine and public health on decreasing death and morbidity rates and on enhancing the population explosion. However, the Symposium emphasizes the reverse effects of socioeconomic changes on health. For instance, construction of trunk roads and development of inland waterways in areas previously isolated may increase the danger of spread of smallpox and other communicable diseases, and construction and use of irrigation systems may increase the incidence of bilharziasis.

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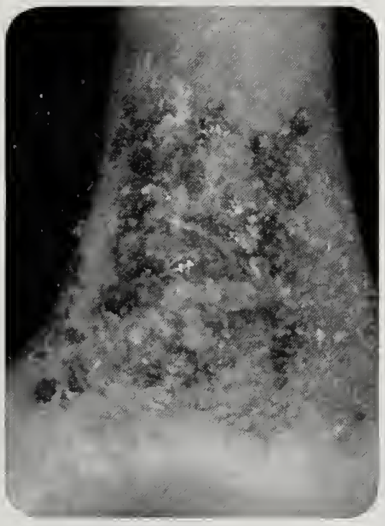

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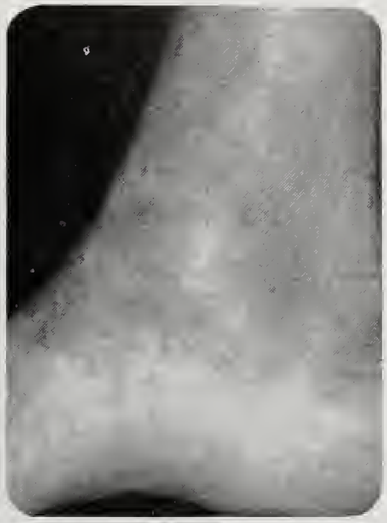

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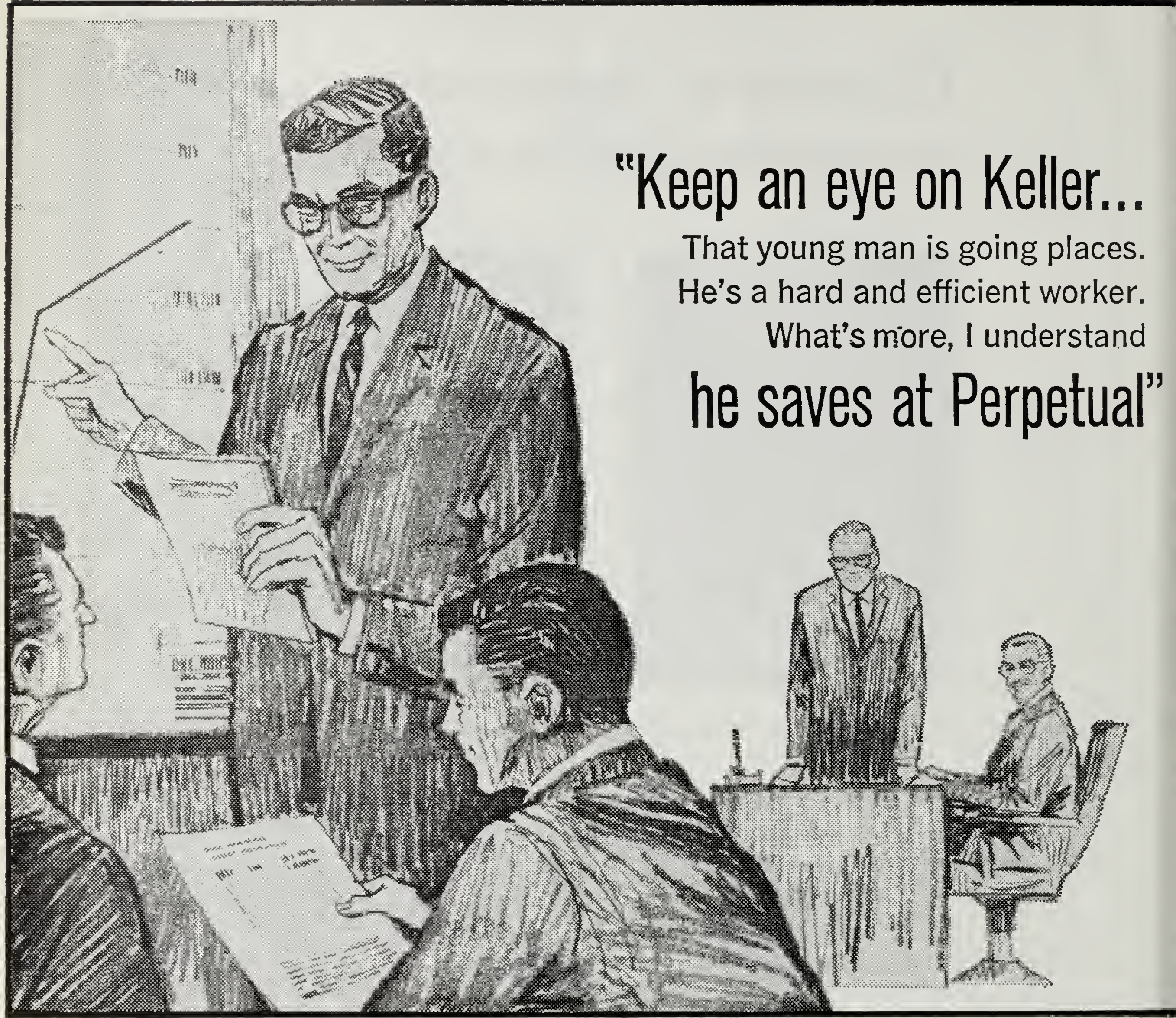
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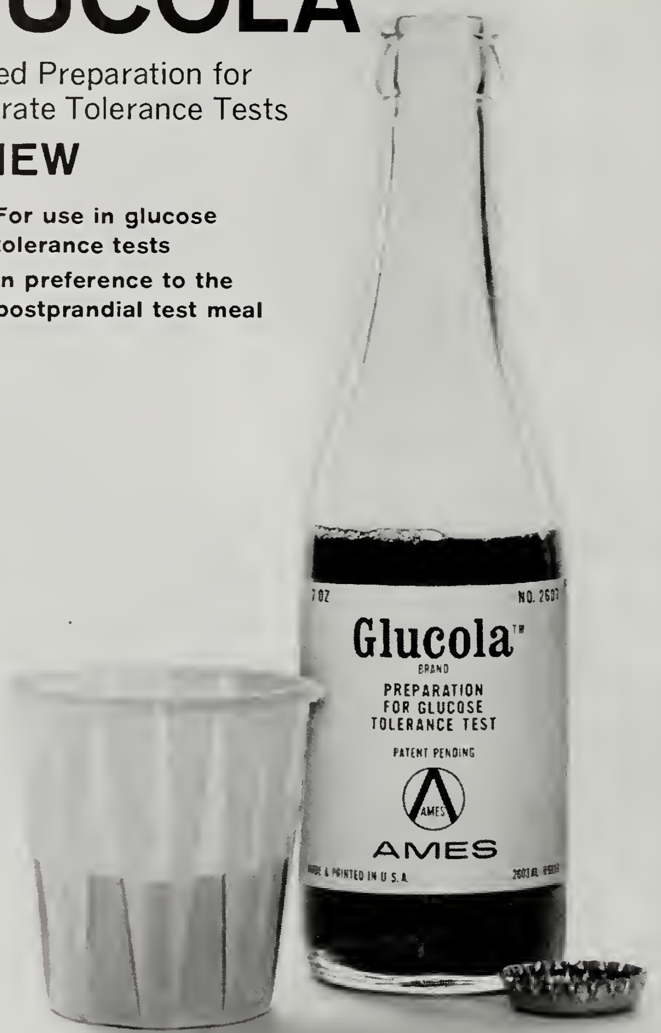

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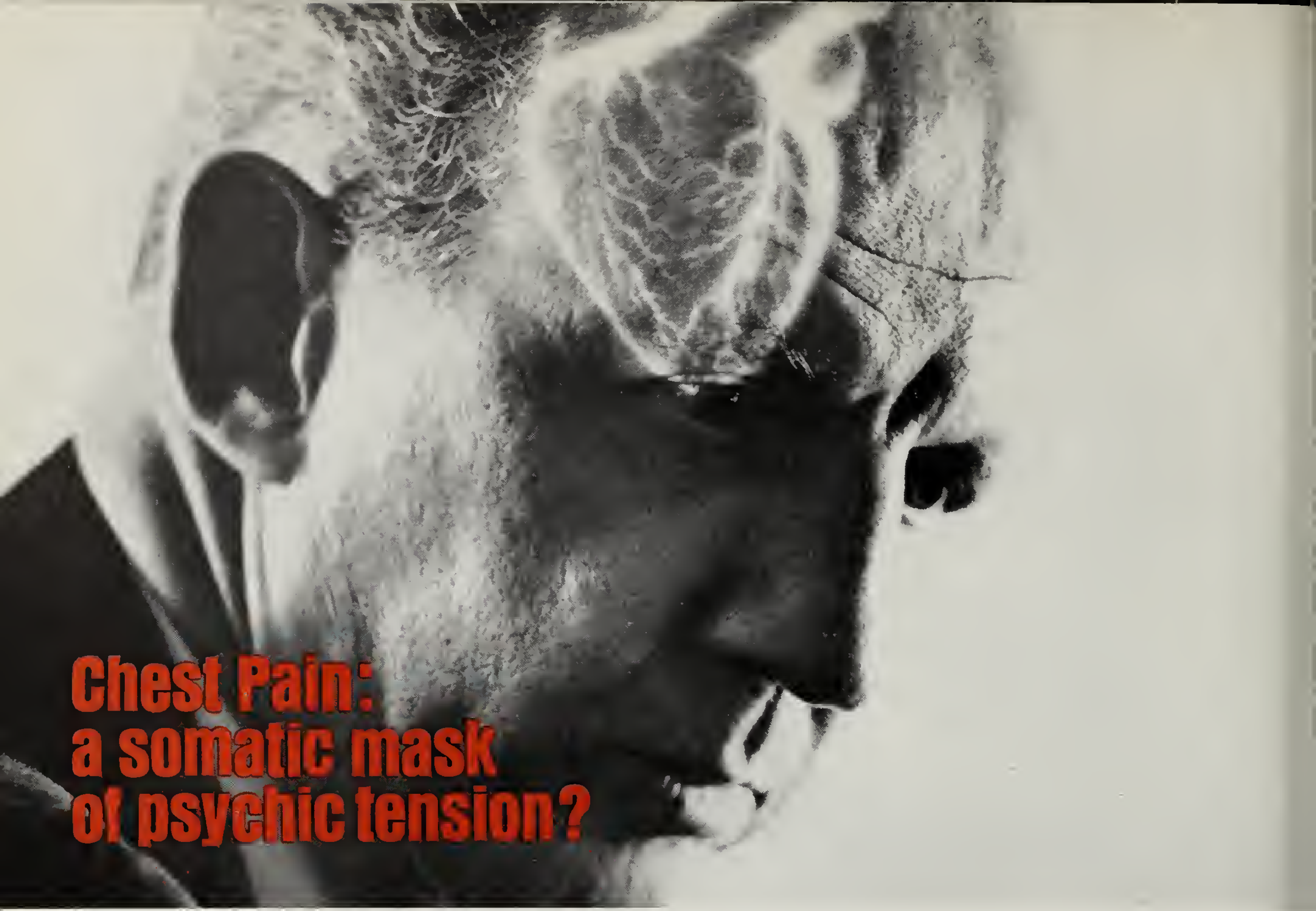

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Precautions: Limit dosage to smallest effective amount in elderly patients (not more than 1 mg, one or two times daily) to preclude ataxia or oversedation. Advise patients against possibly hazardous procedures until correct maintenance dosage is established; driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. Warn patients of possible combined effects with alcohol. Safe use in pregnancy not established. Observe usual precautions in impaired renal or hepatic function and in patients who may be suicidal; periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.

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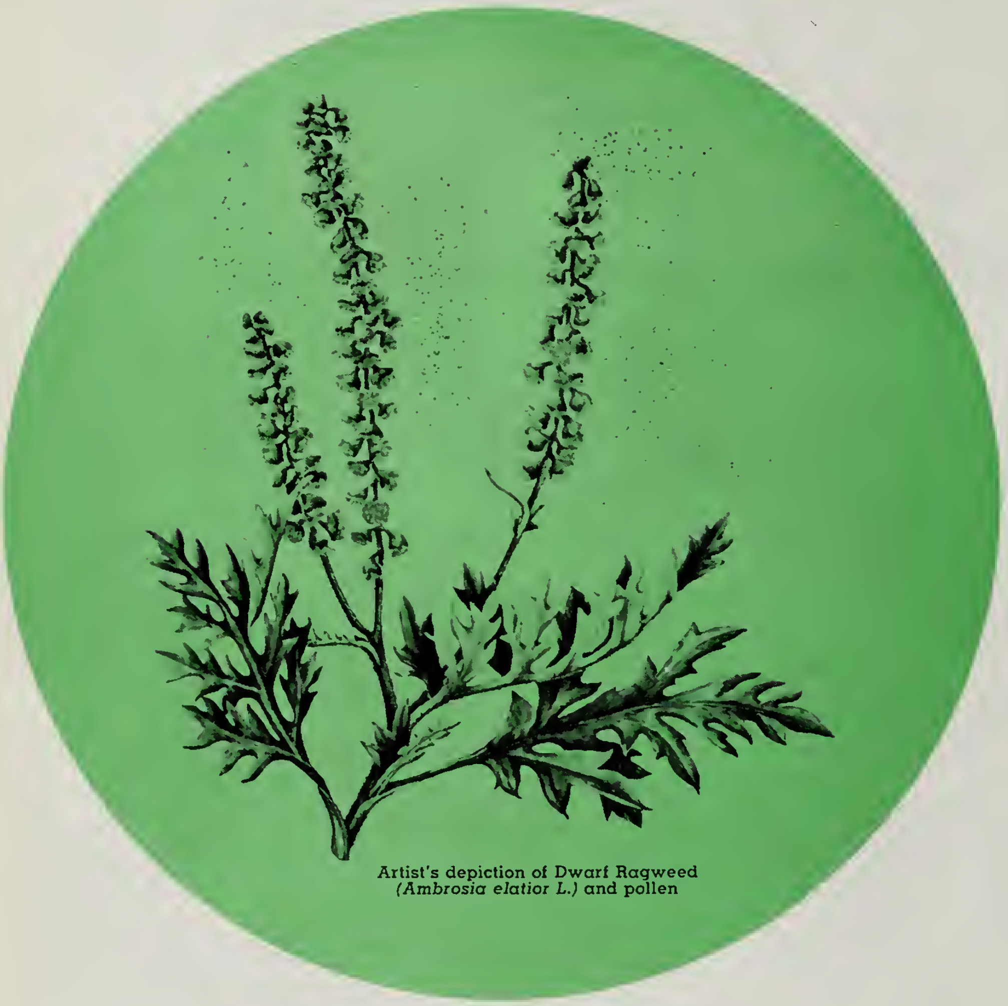

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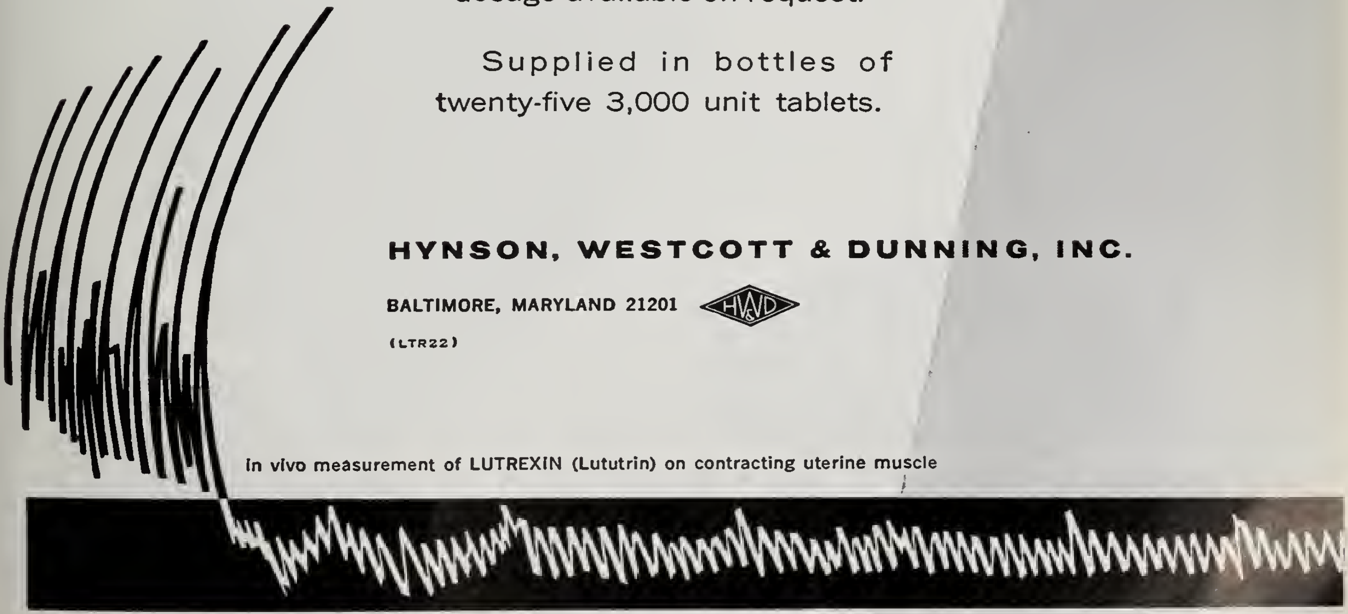

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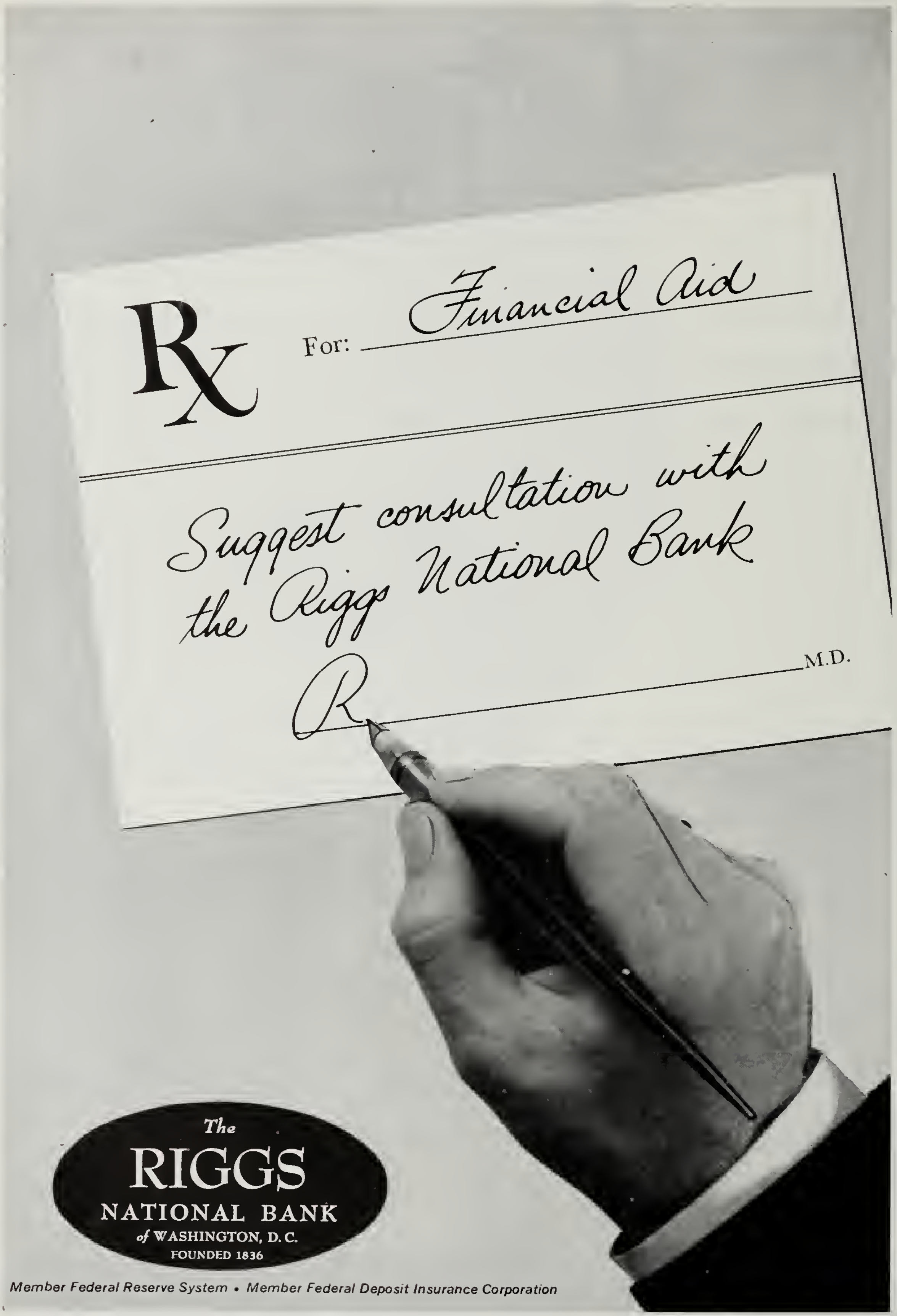

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Side effects: Drowsiness may occur and, rarely, ataxia, usually controlled by decreasing the dose. Allergic or idiosyncratic reactions are rare, generally

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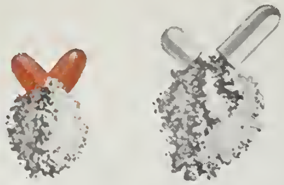

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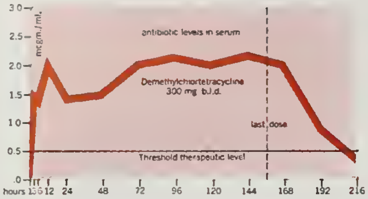
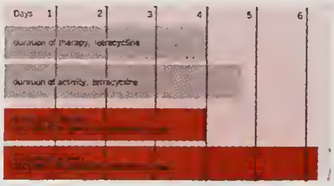


high activity

From Sweeney, W. M., Dornbush, A. C., and Hardy, S. M., Amer. J. Med. Sci. 243:296 (Mar.) 1962



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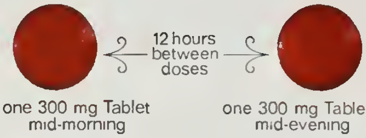

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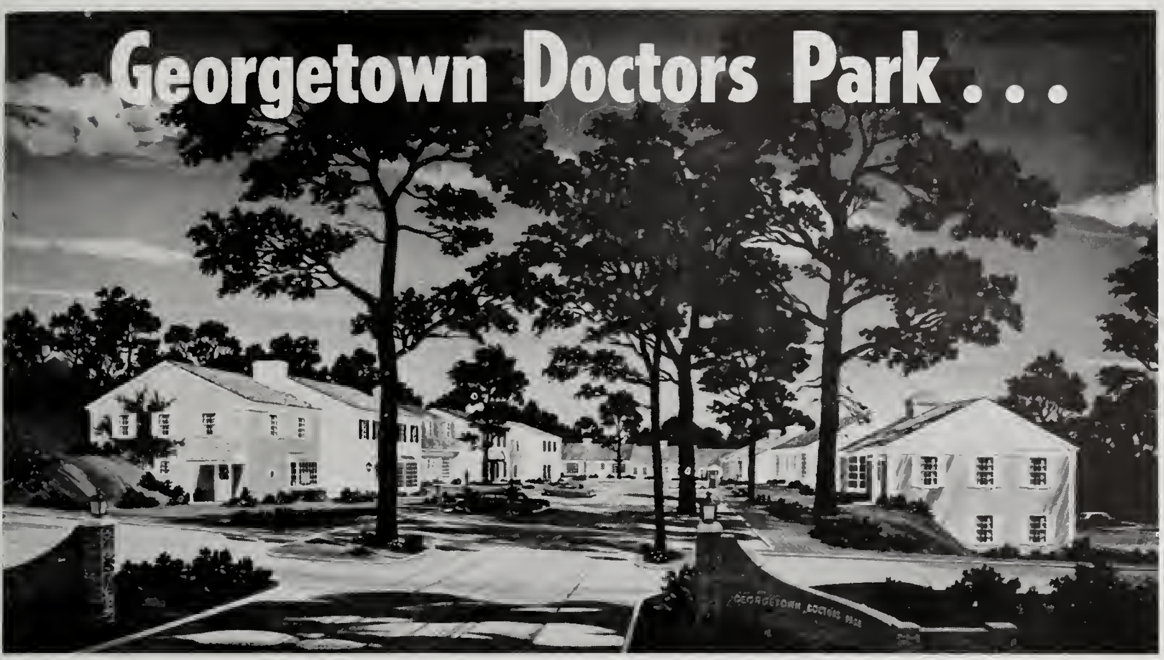

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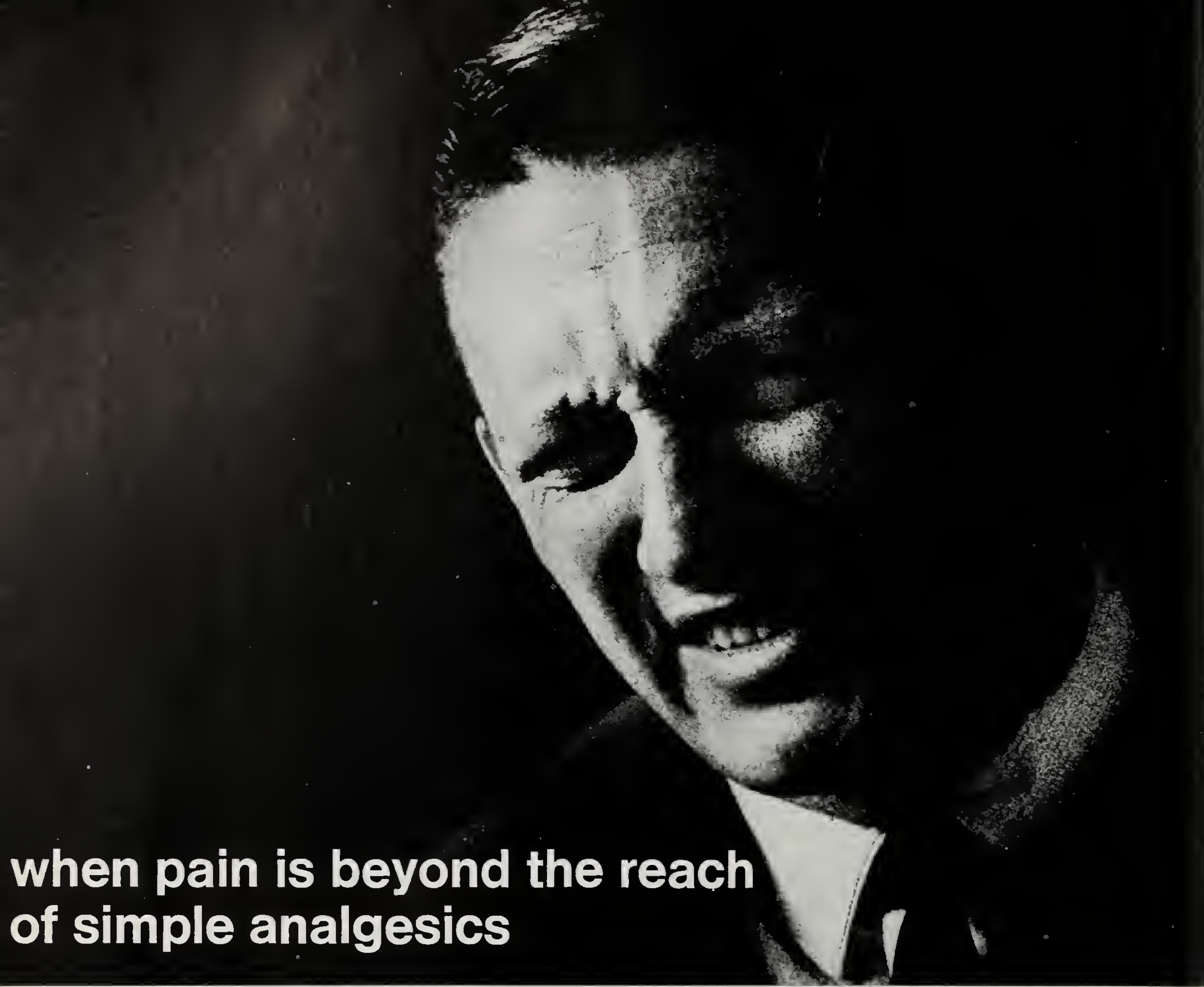
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1. Collective studies, Department of Medical Research, Winthrop Laboratories.

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Reference: 1. Roberts, C. E., Jr.; Perry, D. M.; Kuharic, H. A., and Kirby, W. M. M.: A. M. A. Arch. Int. Med. 107:204 (Feb.) 1961.

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The "Socio-geographic" mystery

Why is one man's gastric ulcer another man's duodenal?

Geographic variation in the *incidence* of peptic ulcer is a familiar fact. But the proclivity of certain *kinds* of ulcer for certain geographic areas is a recently recognized phenomenon.[1,2]

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Social variations, too. Even in the same geographic areas there are interesting variations. An Englishman's ulcer depends on his social standing—professional men suffer with duodenal ulcers, while workingmen have more of the gastric variety. In southern India the pattern is reversed. Here, duodenal ulcers are common among laborers and agricultural workers and rare among the upper classes.

Investigators are exploring every possible theoretical avenue in their search for the cause of peptic ulcer. Of all the factors implicated in ulcerogenesis, the one that is generally acknowledged to be of primary importance is hypersecretion of gastric acid.[3-8] Or, as one author states it: "The medical management of peptic ulcer pharmacologically is, in the final analysis, concerned largely with the effective inhibition of peptic activity."[3]

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References: **1.** Jones, F. A., and Gummer, J. W. P.: Clinical gastroenterology, Springfield, Ill., Charles C Thomas, 1960, pp. 322-3. **2.** Bockus, H. L.: Gastroenterology, 2nd ed., vol. 1, Philadelphia, Saunders, 1963, p. 468. **3.** Sun, D. C. H.: Ann NY Acad Sci 99:153 (Feb. 28) 1962. **4.** Moore, V. A.: Postgrad Med 38:216 (Sept.) 1965. **5.** Dragstedt, L. R., Woodward, E. R., Storer, E. H., Oberhelman, H. A., Jr., and Smith, C. A.: Ann Surg 132:626 (Oct.) 1950. **6.** Posey, E. L., Jr., Smith, P., Turner, C., and Aldridge, J.: Amer J Dig Dis 10:399 (May) 1965. **7.** Lamphier, T. A., Siegel, L., and Goldberg, R. I.: Amer J Gastroent 37:551 (May) 1962. **8.** Kasich, A. M., and Fein, H. D.: Ibid 39:61 (Jan.) 1963. **9.** Epstein, J. H.: Ibid 37:295 (Mar.) 1962. **10.** Moeller, H. C.: Ann NY Acad Sci 99:158 (Feb. 28) 1962. **11.** Slanger, A.: J New Drugs 2:215 (Jul.-Aug.) 1962. **12.** Barman, M. L., and Larson, R. K.: Amer J Med Sci 246:325 (Sept.) 1963. **13.** Shutkin, M. W.: Amer J Gastroent 38:682 (Dec.) 1962. **14.** Fleshler, B.: J New Drugs 2:211 (Jul.-Aug.) 1962.

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September 25–30: III International Congress of Nephrology. Washington Hilton Hotel, Washington. Address: Secretariat, III International Congress of Nephrology, 9650 Wisconsin Avenue, Washington, D. C. 20014.

September 29–October 2: American Medical Writers' Association. Waldorf Astoria, New York. Address: Mr. James E. Bryan, *Executive Director*, 2000 P Street, N.W., Washington, D. C. 20036.

October 1–5: Annual Session of the American Society of Anesthesiologists. Sheraton Hotel, Philadelphia. Address: Mr. J. W. Andes, *Executive Secretary*, 515 Busse Highway, Park Ridge, Ill. 60068.

October 7–8: Tidewater Branch of the Arthritis Foundation and the Norfolk County Medical Society: Arthritis Symposium. Lake Wright Motor Hotel, Norfolk, Va. Address: Mrs. Marcia F. Misel, *Executive Secretary*, 809 Brandon Avenue, Norfolk, Va. 23517.

October 7–8: Congress on Medical Quackery. Pick-Congress Hotel, Chicago. Address: Dr. John G. Thomsen, *Chairman*, American Medical Association, Committee on Quackery, 535 North Dearborn Street, Chicago, Ill. 60610.

October 7–14: American Academy of General Practice. War Memorial, Boston, Mass. Address: Mr. Mac F. Cahal, *Executive Director*, Volker Blvd. at Brookside, Kansas City, Mo. 64112.

October 15: American College of Physicians, District of Columbia-Maryland Regional. D. C. Medical Society Headquarters, Washington. Address: Dr. Thomas W. Mattingly, Washington Hospital Center, 110 Irving Street, N.W., Washington, D. C. 20010.

October 15–16: American Association of Ophthalmology. Palmer House, Chicago. Address: Mr. Lawrence A. Zupan, *Executive Secretary*, 1100 17th Street, N. W., Washington, D. C. 20036.

October 16–21: American Academy of Ophthalmology and Otolaryngology. Palmer House, Chicago. Address: Dr. W. L. Benedict, *Executive Secretary*, 15 Second Street, S. W., Rochester, Minn. 55901.

October 21–25: American Heart Association. Americana Hotel, New York. Address: Mr. Rome A. Betts, *Executive Director*, 44 East 23rd Street, New York, N. Y. 10010.

October 22–27: 35th Annual Meeting of the American Academy of Pediatrics. Palmer House, Chicago. Address: Dr. E. H. Christopherson, *Executive Director*, 1801 Hinman Avenue, Evanston, Ill. 60204.

October 23–26: American College of Gastroenterology. October 27–29: Annual Postgraduate Course. Bellevue-Stratford Hotel, Philadelphia. Address: Mr. Daniel Weiss, *Executive Director*, 33 West 60th Street, New York, N. Y. 10023.

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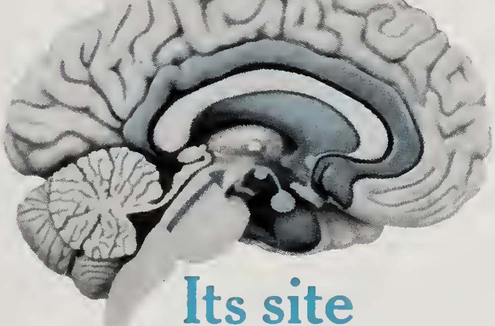

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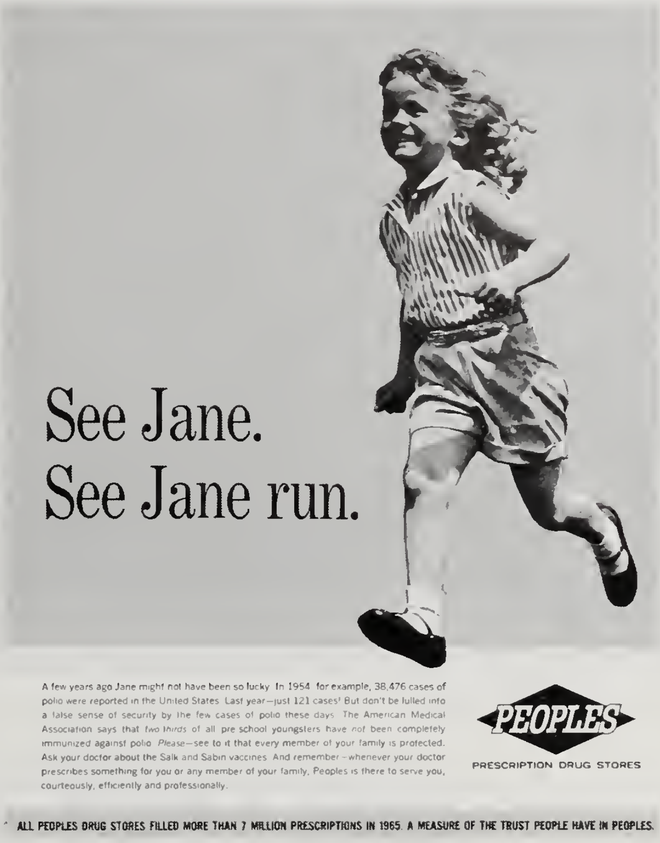

See Jane.
See Jane run.

A few years ago Jane might not have been so lucky In 1954 for example, 38,476 cases of polio were reported in the United States Last year—just 121 cases! But don't be lulled into a false sense of security by the few cases of polio these days The American Medical Association says that *two thirds* of all pre school youngsters have *not* been completely immunized against polio *Please*—see to it that every member of your family is protected. Ask your doctor about the Salk and Sabin vaccines And remember—whenever your doctor prescribes something for you or any member of your family, Peoples is there to serve you, courteously, efficiently and professionally.

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ontraindications
dema; danger of cardiac decompensation;
istory or symptoms of peptic ulcer; renal,
epatic or cardiac damage; history of drug
lergy; history of blood dyscrasia. Because
the increased possibility of toxic reactions,
ıe drug should be used with greater care in
ıe elderly and should not be given when the
atient is senile or when other potent chemo-
ıerapeutic agents are given concurrently.
arge doses of Butazolidin alka are contra-
dicated in patients with glaucoma.

arning
coumarin-type anticoagulants are given
multaneously, the physician should watch
r excessive increase in prothrombin time.

Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Patients receiving such concomitant therapy should be carefully observed for this effect.

Use with caution in the first trimester of pregnancy.

Precautions
Before prescribing, the physician should obtain a detailed history and perform a complete physical and laboratory examination, including a blood count. The patient should be kept under close supervision and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Regular blood counts should be made to guard against blood dyscrasias.

Adverse Reactions
The most common adverse reactions are nausea, edema and drug rash. Moderately lowered red cell count may sometimes occur due to hemodilution. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vertigo or languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia are also possible side effects.

Confusional states, hyperglycemia, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Dosage
The initial daily dosage in adults is 300-600 mg. daily in divided doses. In most instances, 400 mg. daily is sufficient. When improvement occurs, dosage should be decreased to the minimum effective level: this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

For complete details, please refer to full prescribing information.
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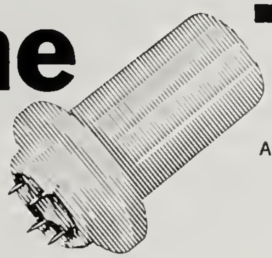

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SQUIBB NOTES ON THERAPY

Breast-feeding and the "modern mother"

Despite a mild resurgence of interest in the importance of breast-feeding a few years ago, many women today do not choose to nurse their young. This is for a variety of reasons—social, economic, cultural and sometimes medical. In such cases the physician's task is to find the most suitable means of preventing lactation and easing the pain of breast engorgement.

The means of therapy

The value of hormone therapy for this indication is of course well established. Both androgen and estrogen are known to inhibit the production and secretion of the lactogenic hormone by the anterior pituitary. As estrogen levels decline sharply at parturition, lactogenesis is established. When androgen and estrogen are administered to the patient before the release of the lactogenic hormone lactation and breast engorgement are usually prevented.

The time of therapy

The time of administration of this combined medication is crucial; it must be given early enough to suppress the pituitary prolactin and last long enough to permit physiologic readjustment during the puerperium. Excellent results are most often seen when therapy is administered before the onset of the second stage of labor.

However, factors other than effectiveness must also be considered. The agent selected should not interfere in any way with parturition, subsequent uterine involution and the restoration of normal ovarian cyclic function. Furthermore, it should not cause rebound breast engorgement or other manifestations of hormonal imbalance.

A balanced formulation

Providing single-dose therapy for the prevention of lactation and breast engorgement, Deladumone OB is a potent androgen-estrogen combination with a prolonged action. The optimal balance of androgenic and estrogenic hormones achieved in this preparation minimizes the disadvantages inherent in single hormone therapy, such as rebound breast engorgement. Involution of the uterus and resumption of menstrual cycles are not affected.

As reported in a recent published study (Roser, D. M.: Obstet. & Gynec. *27*:73, 1966), Deladumone OB provided good suppression of breast engorgement in 95.3% and suppression of lactation in 81.1% of 86 obstetrical patients. These results are in general agreement with those of many earlier investigations; in several studies this injectable androgen-estrogen combination proved to be superior to oral medication.

Dosage:

As a single injection of 2 cc. before the onset of the second stage of labor.

Contraindications:

Established or suspected mammary cancer or genital malignancy.

Precautions and Side Effects:

Certain patients may be unusually responsive to either estrogenic or androgenic therapy. In such individuals virilization, uterine bleeding or mastodynia may occur.

Supply:

Deladumone OB, providing 180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc., is available in 2 cc. Unimatic® disposable syringes and in 2 cc. vials. Both preparations are dissolved in sesame oil, with 2% benzyl alcohol as a preservative. *Before use, consult product literature for full prescribing information.*

Deladumone® OB

Squibb Testosterone Enanthate (180 mg./cc.) and Estradiol Valerate (8 mg./cc.)

Single-dose injection for lactation inhibition

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And 'Stelazine' offers additional benefits. Dependence has not been reported. At low doses, side effects are minimal. Its b.i.d. dosage is convenient and economical.

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brand of **trifluoperazine**

The following is a brief precautionary statement. Before prescribing, the physician should be familiar with the complete prescribing information in SK&F literature or *PDR*. *Contraindications:* Comatose or greatly depressed states due to C.N.S. depressants and in cases of existing blood dyscrasias, bone marrow depression and liver damage. *Precautions:* Use with caution in angina patients and in patients with impaired cardiovascular systems. Antiemetic effect may mask symptoms of other disorders. An additive depressant effect is possible when used with other C.N.S. depressants. Prolonged administration of high doses may result in accumulative effects with severe C.N.S. or vasomotor symptoms. Use in pregnant patients only when necessary for the patient's welfare. *Side Effects:* Occasional cases of mild drowsiness, dizziness, mild skin reactions, dry mouth, insomnia and amenorrhea. Neuromuscular (extrapyramidal) reactions (motor restlessness, dystonias, pseudo-parkinsonism) may occur and, in rare instances, may persist. In addition, muscular weakness, anorexia, rash, lactation, hypotension, and blurred vision have been observed. Blood dyscrasias and cholestatic jaundice have been extremely rare.

For a comprehensive presentation of 'Stelazine' prescribing information and side effects reported with phenothiazine derivatives, please refer to SK&F literature or *PDR*.

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Norinyl® tablets
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for multiple contraceptive action that has produced a record of unexcelled effectiveness

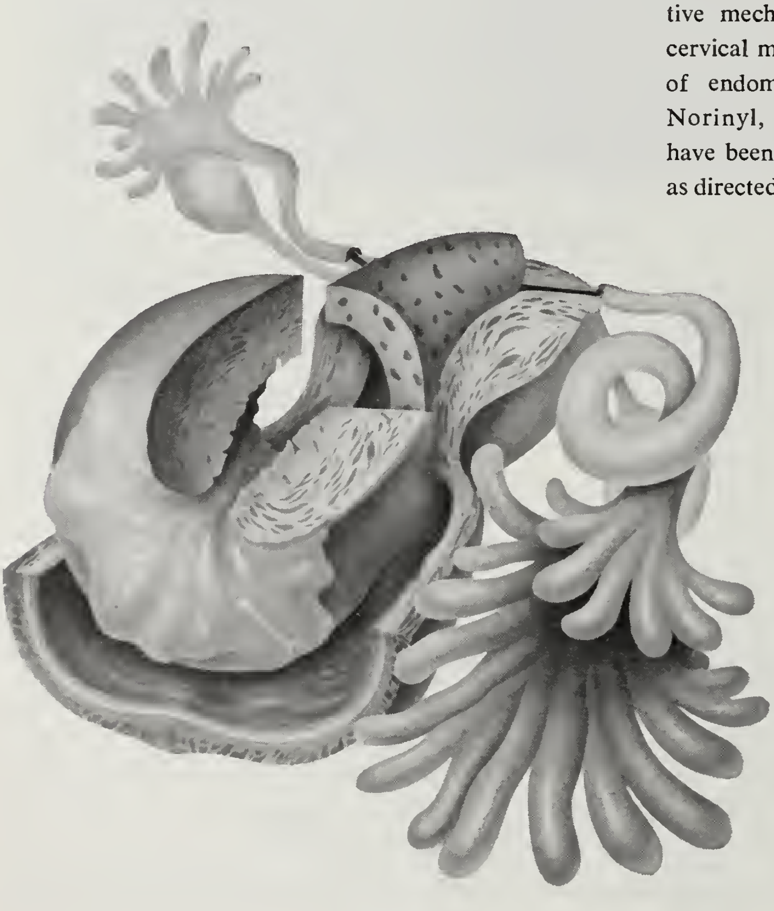
inhibition of ovulation by means of 2 time-proved hormonal agents

production of a cervical mucus hostile to sperm motility and vitality

creation of an endometrium unreceptive to egg implantation

no unplanned pregnancies

Norinyl provides multiple action for maximum assurance of success. It does not depend on ovulation inhibition alone for contraceptive effectiveness. The mechanism of action of combined hormonal therapy results in ovulation inhibition reinforced by other protective mechanisms, including a hostile cervical mucus[1-13] and an acceleration of endometrial changes.[1-3,7-16] With Norinyl, no unplanned pregnancies have been reported to date when used as directed.



plus important supportive benefits that help her through those critical early months of oral contraception

low incidence of side effects

Low incidence of BTB and spotting, nausea and amenorrhea tends to minimize side effect problems and increases patient cooperation.

no confusion about dosage

An unbreakable "confusionproof" package makes it easy to adhere to prescribed dosage schedule: individually sealed tablets numbered from 1 through 20 *plus* monthly calendar record enables patient to double-check dosage intake by day and corresponding tablet number.

NORINYL
2
SYNTEX
T
F
S

Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: **1.** Council on Drugs JAMA 187·664 (Feb 29) 1964 **2.** Bryans, F. E : Canad Med Ass J 92·287 (Feb. 6) 1965. **3.** Goldzieher, J W · Med Clin N Amer 48·529 (Mar.) 1964. **4** Cohen, M R : Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965. **5.** Hammond, D. O.· Ibid. **6.** Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A.: Fertil Steril 14·402 (Jul.-Aug) 1963 **7.** Goldzieher, J W , Moses, L. E , and Ellis, L. T.: JAMA 180:359 (May 5) 1962 **8.** Kempers, R. D.· GP 29 88 (Jan) 1964 **9.** Tyler, E T.· JAMA 187·562 (Feb. 22) 1964 **10.** Rudel, H. W , Martinez-Manautou, J , and Maqueo-Topete, M : Fertil Steril 16:158 (Mar -Apr.) 1965. **11.** Flowers, C E., Jr N Carolina Med J 25:139 (Apr.) 1964. **12.** Goldzieher, J. W Appl Ther 6 503 (June) 1964. **13.** The Control of Fertility. Report adopted by the Committee on Human Reproduction of the American Medical Association JAMA 194·462 (Oct. 25) 1965. **14.** Flowers, C. E., Jr.: JAMA 188:1115 (June 29) 1964. **15.** Merritt, R. I.· Appl Ther 6·427 (May) 1964 **16.** Newland, O. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

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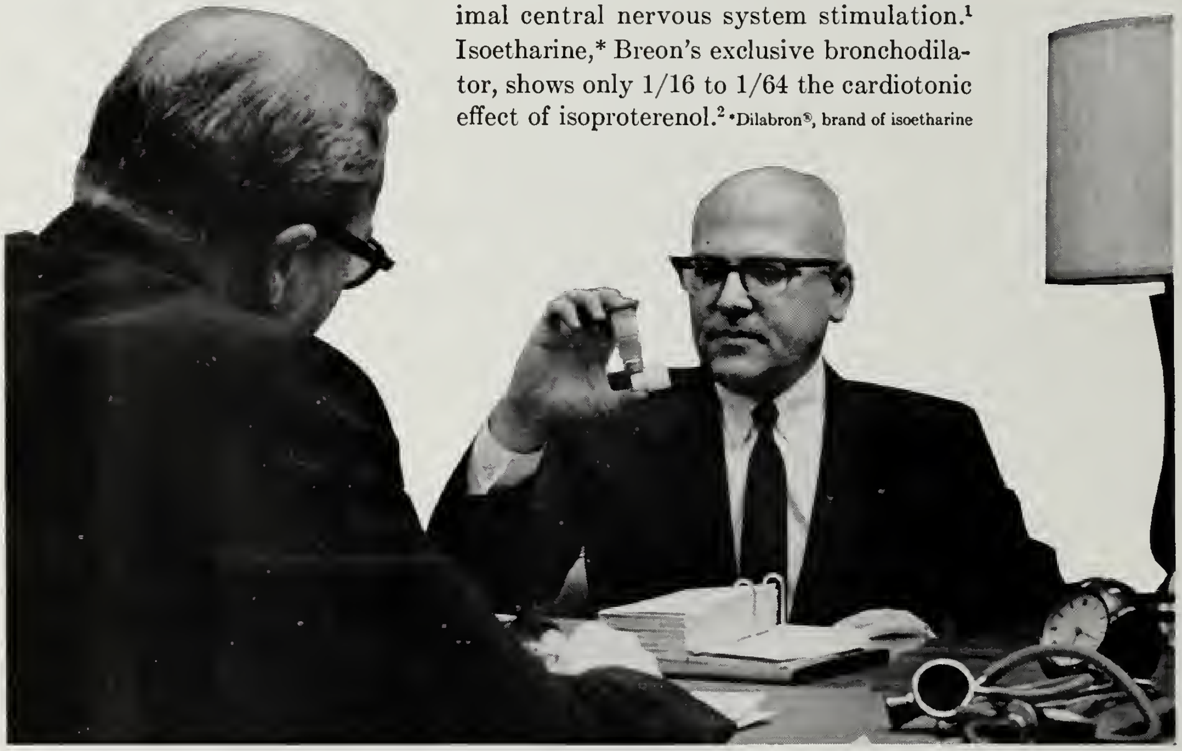

BRONKOMETER® ASTHMA, CHRONIC BRONCHITIS, EMPHYSEMA

isoetharine 0.6%; phenylephrine 0.125%; thenyldiamine 0.05%—Superior because it contains isoetharine

COMPOSITION: Bronkometer delivers at the mouthpiece 200 metered doses of: 350 mcg isoetharine methanesulfonate (0.6%); 70 mcg phenylephrine HCl (0.125%); and 30 mcg thenyldiamine HCl (0.05%) with saccharin, menthol and fluorochlorohydrocarbons as inert propellants. Preserved with ascorbic acid 0.1% and alcohol 30%.

RECOMMENDED DOSAGE: One or two inhalations with at least one minute between inhalations. Occasionally more may be required, however in most cases, inhalations need not be repeated more than every four hours. Dosage should be adjusted to the severity of the condition and to patient's response.

PRECAUTIONS: Bronkometer is unusually free from cardiovascular and other side effects, but the usual precautions associated with sympathomimetic amines should be observed. Bronkometer should not be administered simultaneously with epinephrine or similar compounds because of the possibility of tachycardia, although it may be alternated with these agents. Dosage must be carefully adjusted in patients with hyperthyroidism, hypertension, acute coronary disease, cardiac asthma, limited cardiac reserve and in individuals sensitive to sympathomimetic amines.

SUPPLIED: 10 ml pressurized aerosol vials complete with measured dose valve and oral nebulizer.

References: 1. Spielman, A. D.: *Curr. Therap. Res.* 3:235 (June) 1961. 2. Herschfus, J. A.; Bresnick, E.; Levinson, L.; and Segal, M. S.: *Ann. Allergy* 9:769 (Nov.-Dec.) 1951.

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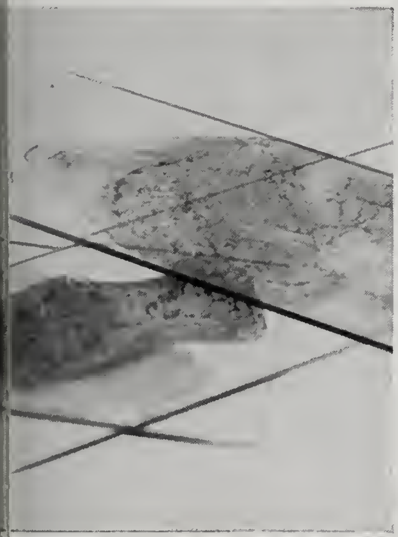
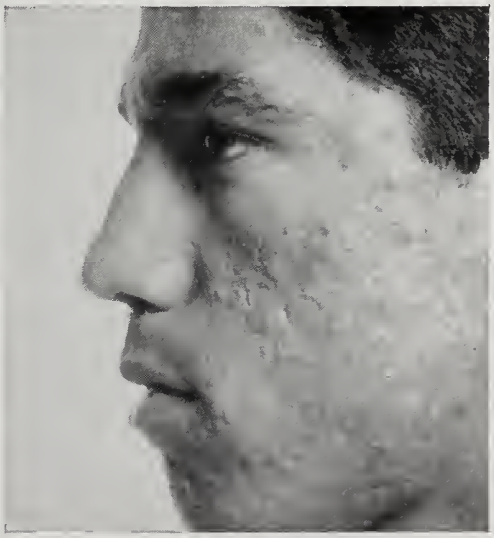


5. patients on long-term tetracycline or corticosteroid therapy



BRISTOL THERAPEUTIC SUMMARY: For complete information consult Official Package Circular. *Indications:* Infections of respiratory, gastrointestinal and genitourinary tracts and skin and soft tissues due to tetracycline-sensitive organisms, in patients with increased susceptibility to monilial infections. *Contraindications:* The drug is contraindicated in patients hypersensitive to its components. *Warnings:* Photodynamic reactions have been produced by tetracyclines. Natural and artificial sunlight should be avoided during therapy. Stop treatment if skin discomfort occurs. With renal impairment, systemic accumulation and hepatotoxicity may occur. In this situation, lower doses should be used. Tooth staining and enamel hypoplasia may be induced during tooth development (last trimester of pregnancy, neonatal period and childhood). *Precautions:* Bacterial superinfection may occur. Infants may develop increased intracranial pressure with bulging fontanels. In gonorrheal therapy, serologic tests for syphilis should be conducted initially and monthly for 3 months. *Adverse Reactions:* Glossitis, stomatitis, nausea, diarrhea, flatulence, proctitis, vaginitis, dermatitis, and allergic reactions may occur. *Usual Adult Dosage:* 1 capsule *q.i.d.* Continue therapy for 10 days in beta-hemolytic streptococcal infections. Administer one hour before or 2 hours after meals. *Supply:* Capsules, bottles of 16. Each capsule contains tetracycline phosphate complex equivalent to 250 mg. tetracycline HCl activity and 250,000 units of nystatin.

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Indications: 'Soma' is useful for management of muscle spasm, pain, and stiffness in a variety of inflammatory, traumatic, and degenerative musculoskeletal conditions. It also may act to normalize motor activity in certain neurologic disturbances.

Contraindications: Allergic or idiosyncratic reactions to carisoprodol.

Precautions: 'Soma', like other central nervous system depressants, should be used with caution in patients with known propensity for taking excessive quantities of drugs and in patients with known sensitivity to compounds of similar chemical structure, e.g., meprobamate.

Side Effects: The only side effect reported with any frequency is sleepiness, usually on higher than recommended doses. An occasional patient may not tolerate carisoprodol because of an individual reaction, such as a sensation of weakness. Other rarely observed reactions have included dizziness, ataxia, tremor, agitation, irritability, headache, increase in eosinophil count, flushing of face, and gastrointestinal symptoms.

One instance each of pancytopenia and leukopenia, occurring when carisoprodol was administered with other drugs, has been reported, as has an instance of fixed drug eruption with carisoprodol and subsequent cross reaction to meprobamate. Rare allergic reactions, usually mild, have included one case each of anaphylactoid reaction with mild shock and angioneurotic edema with respiratory difficulty, both reversed with appropriate therapy. In cases of allergic or hypersensitivity reactions, carisoprodol should be discontinued and appropriate therapy initiated. Suicidal attempts may produce coma and/or mild shock and respiratory depression.

Dosage: Usual adult dose is one 350 mg. tablet three times daily and at bedtime.

Supplied: Two Strengths: 350 mg. white tablets and 250 mg. orange, two-piece capsules.

Before prescribing, consult package circular.

for the relief of low back sprains and strains

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(CARISOPRODOL)

Wallace Laboratories, Cranbury, N.J.

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now...specific therapy for night leg cramps

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Consistently effective, QUINAMM provided complete relief in 94% of 200 patients studied, many of whom were severe cases refractory to other medication.[3] Your prescription for one tablet at bedtime often controls painful night cramps with the initial dose . . . helps restore restful sleep.

QUINAMM Prescribing Information: Composition: Each white, beveled, compressed tablet contains: Quinine Sulfate 4 grains (250 mg.) and Aminophylline 3 grains (200 mg.). **Precautions:** Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. **Contraindication:** QUINAMM is contraindicated in pregnancy because of its quinine content. **Dosage:** One tablet upon retiring. Where necessary, dosage may be increased to one tablet following the evening meal and one tablet upon retiring. **Supplied:** Bottles of 100 and 500 tablets. **Caution:** Federal law prohibits dispensing without prescription.

References: 1. Shuman, C.: Am. J. Med. Sci., 225:54, 1953. 2. Perchuk, E., et al.: Angiology, 12:102, 1961. 3. Rawls, W., et al.: Med. Times, 87:818, 1959.

WALKER Laboratories Division of Richardson-Merrell Inc., Mount Vernon, New York 10551

summer 1966

DORSEY Season

A journal within a journal published quarterly in the interests of better medicine by Dorsey Laboratories, a division of The Wander Company, Lincoln, Nebraska. Address communications to Raymond C. Pogge, M. D., Director of Medicine.

this issue: emergency anesthesia and the common cold

When emergency anesthesia is complicated by the common cold

Barry Belonsky, M.D., F.A.C.A.
Staff Anesthesiologist, Hospital of The Albert Einstein College of Medicine, New York City

Medical facilities are often presented with unfamiliar patients who have unknown health histories. This is particularly true in emergency situations that arise due to accidents or acute illnesses. These cases may need prompt care requiring anesthesia, and if they involve colds, nasal allergies or other upper respiratory infections, can account for many complications which make up a major hazard during emergency anesthesia.

Administration of general anesthesia to a patient with a cold or upper respiratory infection is a hazardous undertaking. It should be avoided if at all possible. Indeed, the presence of U.R.I. is good reason for postponement of elective surgery.[1] In emergency surgery, regional or local block should be considered, but if general anesthesia is mandatory, it should be approached with utmost caution.

Since the attitude of "emergency surgery — hurry" has been replaced by "emergency surgery — watch out",[2] a knowledge of the complications is a great help in preventing them. Here is a brief outline of the problems involved and their treatment. Prevention of the complications is discussed later.

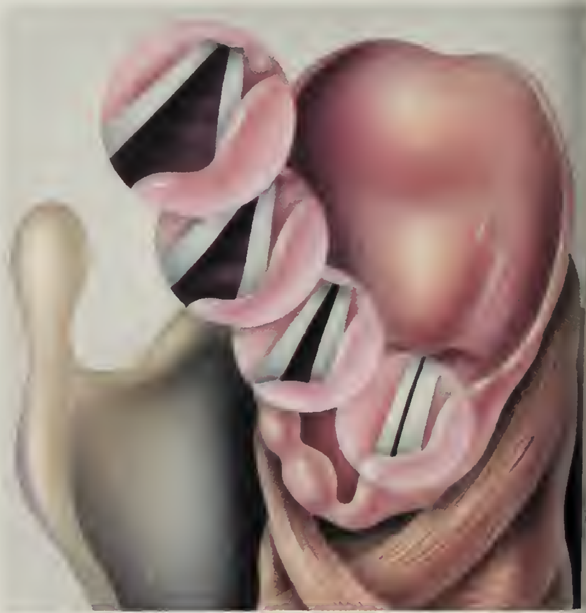
Complications during the induction of anesthesia

Most of the complications are a direct result of secretions and some a result of accompanying secondary infection. For example, *airway obstruction* due to excessive secretions occurs very commonly and is the direct effect of the cold. Respiratory exchange may be obstructed at any time during anesthesia because of excessive secretions, but is most likely to occur during induction. Suction apparatus must be available to overcome this.[3]

Excess secretions which stimulate and irritate the epiglottis and vocal chords can cause *laryngeal stridor and obstruction.* This can lead to complete laryngeal closure with resultant anoxia and death. *Bronchospasm and laryngospasm* can result fron secretions penetrating the bronchi and bronchiole In laryngospasm, there are both inspiratory and e piratory stridor and difficulty in inflating the chest in bronchospasm there is an expiratory wheeze, bu not as much difficulty in inflation, although som resistance may be felt. Stridor is due to partial o complete closure of the vocal cords in spasm and th "crowing" sound is almost pathognomonic.

Secretions obstruct the nasal airways. This produce *difficulty in ventilation* through the mouth until th patient is deep enough to place an oral airway. A intravenous agent can be given to facilitate the i duction of anesthesia.

Difficulties can arise if intubation is performed t ventilate the patient. For example, teeth can b broken by too vigorous attempts at intubation, c the intubation itself may be technically difficult du to secretions obstructing the view of the glottis. Th postoperative sequelae of intubation ranges fro mild laryngitis to pneumonia with atelectasis, an are seen far more commonly in patients sufferin from colds than in normal patients.



Successive stages of laryngospasm which produce the c acteristic stridor or "crowing" sound.

Progression of bronchioles into bronchospasm.

Complications during the maintenance of anesthesia *Bronchospasm* can occur in an unintubated patient due to secretions entering the bronchial tree from above, and acting as an irritant to the bronchi and bronchioles. Secretions accumulate quickly and the patient has to be suctioned continually. The whole cycle of coughing, bucking, laryngospasm and bronchospasm may ensue. The difficult decision here is whether it is better to suction the patient continually or to use an endotracheal tube which protects the cords and bronchi but introduces the risk of attendant complications.

Postoperative complications Postoperatively, complications can be more serious than even the intra-anesthesia complications, and occur much more frequently in a patient who has been intubated.[4]

Sore throat and pharyngitis can result both from the preoperative upper respiratory infection and from the drying of the mucous membranes which occurs during anesthesia.

Tracheitis and bronchitis often result from secretions trickling down the tracheobronchial tree.

Laryngitis is frequently seen in patients with upper respiratory infections who have been intubated. There is a significant increase in the incidence of laryngitis compared to that in patients without upper respiratory infections.

Subglottic edema is a condition which occurs mainly in children who have been intubated. This pathology results from an exudate developing in the areolar tissue just below the cords. Because of the small size of the child's trachea, even a 1 mm increase in size of the mucous membrane can severely impair the air passage. Children exhibit this by severe expiratory stridor and may even become cyanotic. This may so severely embarrass the child's breathing that it must be treated vigorously. Most authorities agree on the treatment[5,6,7,8] consisting of a high oxygen concentration in the inspired air (60%), plus high humidity (close to 100%). Adequate parenteral fluid intake and slight cooling of the body temperature (by a cooled oxygen tent) also help in mild cases. In severe cases, there may be hypoxia which increases the restlessness and the oxygen demand rises. Sedation is often necessary, although concomitant depression of the respiratory center is undesirable. An antihistaminic accomplishes this purpose well, and adds sedation. Since there is always a possibility that an allergic response plays a role in edema, some relief of the respiratory distress may occur. Steroids should be used to control inflammatory and allergic phenomena and swelling. If all this fails, and the patient is still restless and hypoxic, a tracheostomy should be performed immediately.

(concluded on following page)

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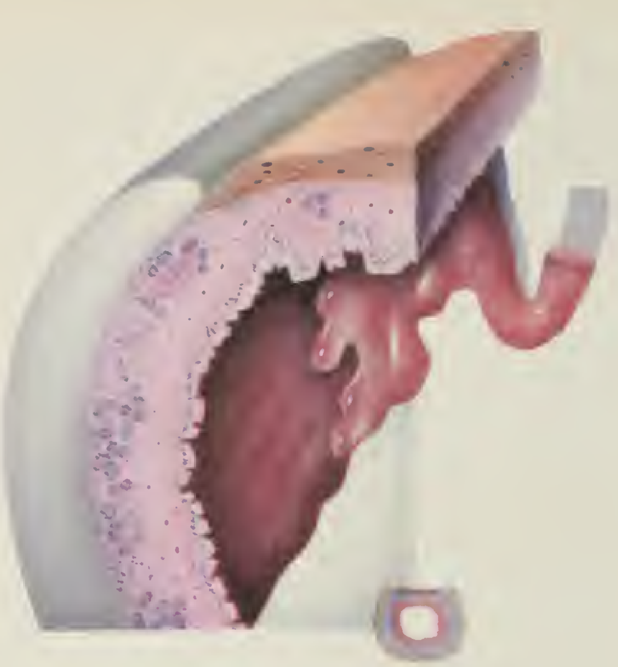

Cross section of trachea showing subglottic edema and lumen reduction due to mucous membrane congestion.

Pneumonia may also follow anesthesia administered to a patient with a cold. This can be caused by accumulated secretions becoming secondarily infected and causing consolidation of the lung. *Atelectasis* of the lung can result if one of the bronchioles becomes plugged by secretions, preventing aeration of the distal part of that lung. This is seen more frequently following upper respiratory infection because dry anesthetic gases aggravate the infection, causing secretions to change from watery to thick and viscid, and consequently difficult to suction.

Prevention of complications The first rule to prevent complications, of course, is to use a regional or local anesthesia whenever possible. But when emergency surgery is a must, in spite of the presence of a cold, allergy, or upper respiratory infection, here are some ways to prevent complications.

Give nose drops preoperatively. This can help shrink the congested nasal mucous membranes and reduce secretions for better air passage. (Results of this method are sometimes unsatisfactory because of the short duration of effect or rebound congestion.) For longer effect, oral antihistamines with nasal decongestants are often given to provide and maintain a drying effect on secretions.

To clear the tracheobronchial tree, instruct the patient to cough preoperatively. Cold steam or water nebulizers effectively humidify the nasal, pharyngeal and bronchial passages and often make the patient more comfortable. Tenacious secretions become more watery under humidification, clear more thoroughly preoperatively and are more easily suctioned from the airway during anesthesia.

Give intravenous fluids to those patients who appear dehydrated due to a cold. In a well hydrated patient the respiratory tract secretions are less viscid and more watery. This is particularly true in asthmatics.

Summary: Administration of emergency anesthesia to a patient with a cold or upper respiratory infection can lead to a chain of events that may result in increased postoperative morbidity and even death. This is because of the excess secretions formed in these conditions. Preoperative measures to prevent or reduce these secretions should be undertaken and will result in smoother and safer anesthesia.

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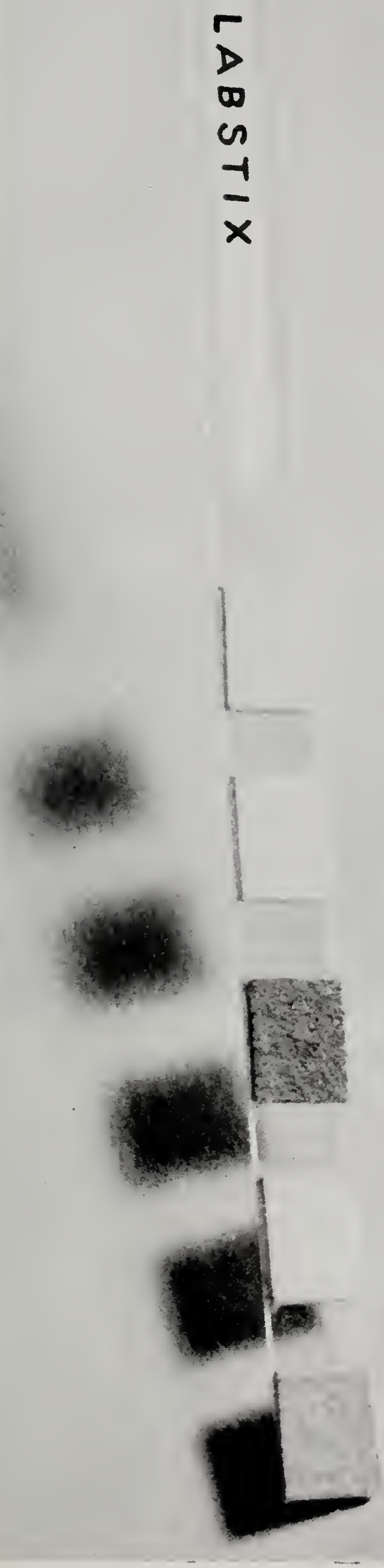

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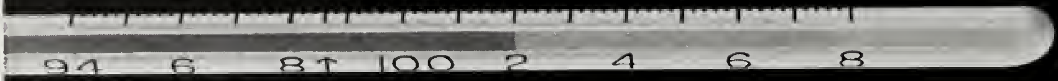

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MEDICAL ANNALS

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September 1966 VOLUME XXXV • NUMBER 9

Georgetown University Medical Center Number

It is fitting that this third Georgetown University Medical Center Number of the Medical Annals be dedicated to the current President of the D. C. Medical Society, Dr. Robert J. Coffey. Each of the papers presented in this issue is from a separate Division of the Department of Surgery, of which Dr. Coffey is the Chairman and Professor. These papers indicate the growth of the Department of Surgery that has taken place in the 20 years that Dr. Coffey has been the Chairman. When he started at that post it was, for all practical purposes, a one-man show. Each of the Divisions represented by these papers has been added during Dr. Coffey's tenure.

More accurately than material things does the growth of a Department demonstrate true progress in a Medical Center. The quality of the people and the work that they do are keener reflections of advancement than such criteria as the number of buildings and the amount of money in a budget. The character of the staff that a Chairman gathers about him truly reflects his own ambitions and desires. The products of these individuals indicate why national and international acclaim have come to this Department.

On a personal note, in my many years of association with Robert I have found in him the highest degree of integrity, the wisdom of an experienced clinical surgeon, and an unfailing sense of humor.

Irving B. Brick, M.D.
Professor of Medicine. Georgetown University School of Medicine

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Cardiac Valve Replacement—Its Current Status

CHARLES A. HUFNAGEL, M.D., F.A.C.S.*, JOHN F. GILLESPIE, M.D.†, PETER W. CONRAD, M.D., F.A.C.S.†, CLAUDE MERCIER, M.D.‡, AND CAPTAIN FELIX A. EVANGELIST, USAF, MC‡

Prior to 1952 no serious thought was given to the replacement of a moving part of the cardiovascular system by materials of nonbiologic origin. The first successful clinical application of the ball valve principle and the introduction of the concept of inhibition of in vivo blood clotting by plastic surfaces marked the beginning of a new era in the treatment of cardiovascular disorders.[1] For the first time definite therapy of these diseases became possible by the replacement of heart valves and major blood vessels (figure 1). Since that time there have been many developmental changes and major reinforcements of techniques. The principal areas in which there has occurred a rapid accumula-

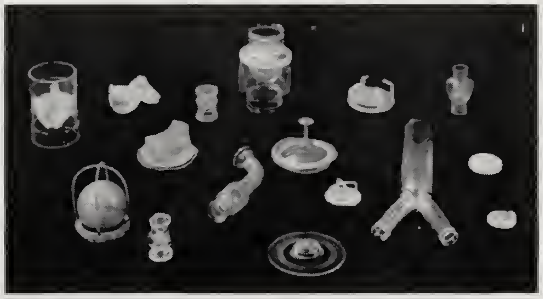

FIG. 1. Original valve models and arterial replacements.

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tion of knowledge have been (1) in the natural history of disease processes themselves, (2) the clarification of etiology and the pathologic changes which are produced by etiologic factors, (3) the selection of patients based on the knowledge of the foregoing points, (4) a better understanding of the preoperative management of the patient, (5) improvement in the understanding of the physiology of extracorporeal circulation and the management of the patient, (6) improvement of valve design, and (7) major advances in the immediate postoperative care of the patient.

Studies of the natural history of various forms of valvular disease have led to a deeper understanding of the hemodynamics of individual lesions and combinations of lesions. As a result of these studies it is possible to anticipate with a considerable degree of accuracy the amount of improvement which can be expected from operations, and to determine those patients in whom the risk of operation is greater than usual. Those patients with valvular disease in whom there is an additional superimposed element of myocardial disease may be detected only by special studies such as coronary angiography and cardiac catheterization. As would be expected, those patients who have significant degrees of myocardial fibrosis and diffuse coronary artery disease carry an increased risk. However, in those patients whose lesions seriously impede the cardiac output but which can be corrected by operation, coronary artery disease does not necessarily constitute a contraindication to operation. Patients who have chronic congestive failure which has been present for prolonged periods of time and who show great elevation of the end diastolic pressure in the left ventricle also go into a high risk group. This is particularly true of those patients who have a greatly reduced cardiac output as well. Patients who have primarily aortic valvular disease and who show much pulmonary hypertension as an associated feature have also been demonstrated to be in the higher risk category.

Quantitative assay of the left ventricular reserve remains a difficult problem in some cases, but renewed efforts are being made to find satisfactory ways to determine which patient has totally inadequate reserve for operation. The need for earlier decision in relation to operation is apparent, since a large percentage of patients who come to operation fall into the high risk category and have given evidence of serious difficulty for a considerable period of time. It is important to note that even patients in the advanced group have demonstrated an excellent physiologic improvement when they can be satisfactorily carried through the immediate postoperative period.

Many modifications have been made in the technique of extracorporeal circulation which enables it to be performed with a minimum risk to the patient. At the present time it would be extremely rare to encounter a complication which is directly related to the technique of extracorporeal circulation or to inadequate perfusion during the period of cardiopulmonary bypass. The use of hemodilution with adequate buffering solutions, the use of mannitol, and high flow rates of perfusion all contribute to the safety of the method. When the aortic root must be isolated as for replacement of the aortic valve, coronary perfusion of 1 or both coronaries has been almost universally adopted. The use of flexible silicone rubber catheters which are self inflating has markedly simplified the techniques of coronary perfusion.[2]

As a result of the experience which has been obtained over the past 14 years many modifications of valvular mechanism have been employed for the aortic, mitral, and tricuspid positions. The ball valve,[3] which has been widely employed, has made possible the replacement of valves which were not susceptible to any reconstructive procedures and has functioned satisfactorily for long periods of time. There have been, however, intrinsic problems which have been well recognized in the use of ball valve prosthesis, and much research has been directed toward the alteration of valve designs to overcome these difficulties. As a result of these studies it is our opinion that the newer concepts have rendered this design obsolete.

Since 1962 we have employed a discoid type of prosthesis which had been developed during the period between 1960 and 1962.[4] Since the beginning of its clinical use several modifications have been introduced which have been made to further improve the hemodynamics of flow.

The body and disc of this valve are made of polypropylene (figure 2). Polypropylene was selected for the construction of this prosthesis because of its extremely light weight, flexibility, great resistance to impact and wear, little water absorption, and extremely low biologic reactivity. Each of these characteristics has a relationship to the desirable qualities sought for in artificial valvular replacement. In all valvular replacements which employ the principle of moving an obstructive part to prevent backflow there is a tendency for the prosthesis to be displaced by the striking force of the moving part. This tendency for dislodgment and torsion which produces severe strain upon the suture line is a direct function of the mass of the moving section and the distance over which it travels. Thus, the greater the weight of the moving part, the greater the force exerted on striking the valve seat in the closed position.

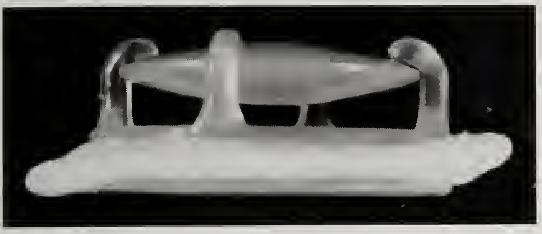

FIG. 2. Polypropylene discoid valve.

In the ball valve prosthesis the diameter of the ball must of course be equal or greater than the valve orifice in order to insure adequate closure. Thus, the valve stops must protrude for a considerable distance beyond the valve seat, since the ball must travel for a distance at least equal to its radius in order to achieve complete opening of the mechanism. This results in a valve of considerable length with protrusion into the aorta or ventricle for a long distance.

The discoid valve, however, can achieve the complete opening with a travel of 5 to 6 mm. even with a large orifice of 25 mm. diameter. Because of the very light weight of material (polypropylene has a specific gravity of less than 1) and because of the short distance necessary for complete opening, an extremely rapid response is achieved. The valve closes and opens very rapidly, since there is little inertia and the distance the disc moves is very short. The impact of opening and closing is negligible because of the small mass and short travel. The total weight of the disc valve is less than one fifth of a ball valve of similar size. The valve stops in the open position are provided by rounded posts seated 90 degrees apart throughout the circumference so that the amount of extraneous material is reduced to a minimum.

The base of the valve housing is particularly important in valve design. The valve cuff in most of the presently available ball valves is attached to the housing in such a way as to be essentially continuous with it. Ingrowth of tissue into the cuff under these circumstances can continue to extend over onto the valve seat and thus interfere with opening and closing of the valve as an initial event. Following this, tissue growing over the cuff and onto the valve base tends to lose its blood supply, becomes necrotic, liberates thrombogenic materials, and produces tissue or thrombotic emboli. The valve housing as it is constructed in this new valve mechanism presents an abrupt shoulder of 3 mm. in height extending upward and downward from the tissue-impervious "Hepacone"-coated cuff.[5] Thus, any tissue growth which may occur has been shown experimentally to be blocked by the impervious cuff and the vertical edge of the housing. Tissue cannot extend into the mechanism and the formation of a tissue pannus is eliminated. An additional feature of the new design is that the opening of the valve orifice is gradually tapered in both directions to provide smooth continuity of the changing direction of blood flow.

The curvature of the surface of the disc and the shape of the proximal and distal sections of the disc have been under study in the laboratory for some time. High-speed photographic studies (350 to 2,000 frames per minute) in the pulse duplicator are being used to determine the optimal shape of the disc to produce minimal turbulence in flow and at the same time maintain the highly advantageous characteristics of the thin disc. The shapes shown in figure 3 show some of the variants which are being studied. Preliminary studies to date tend to indicate that in the mitral position the simple, flat disc is highly satisfactory, and the same has been true in the aortic position. It would appear, however, that some modifications of the disc shape would improve the flow characteristics particularly in the aortic position. A disc of a modified shape which will present a slightly more rounded face on the proximal or inlet side of the valve and a short conical section on the distal or outlet side of the valve appears to give improved flow characteristics. Dynamic studies are being made to delineate this problem fur-

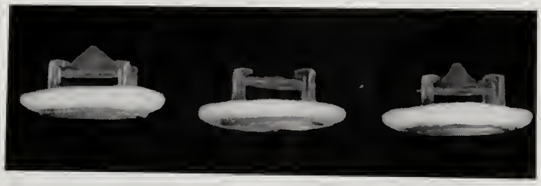

FIG. 3. Designs of discs evaluated for flow characteristics.

ther. It is quite evident, however, that from the practical point of view, in both clinical use and from the experimental data compiled at the present time, the disc as it has been employed clinically in over 100 cases has been a highly efficient, satisfactory mechanism.

A number of methods have been proposed for the fixation of the artificial valve into the normal anatomical position. We have continued to use a short, flat cuff of approximately 3 to 4 mm. in width. In the early work problems of clotting of the cuff were encountered in all types of valvular prostheses including the ball valve, disc valve, and leaflet types. In an effort to eliminate this the problem has been extensively studied in the research laboratory. As a result of work to develop a material which is highly resistant to clotting we have evolved 2 new materials which have not previously been known.

The first of these is a combination of heparin and silicone rubber which we have called "Hepacone," and the second is a combination of silicone rubber, colloidal graphite, and heparin which has been called "Hepacone-G." In order to determine the efficiency of these materials in preventing clot formation the right atrium of the dog was selected as the test site. Small implants of different materials of identical size and shape were placed into the right atrium of the dog. When the implants used were of Teflon®, silicone rubber, silicone rubber plus graphite, or the various types of Teflon and Dacron® cloth which are used for cuff materials, clotting uniformly occurred within 2 hours and entirely covered each of the implants (figure 4). Tests were then made with various formulations of "Hepacone" and "Hepacone-G." These materials have now been evaluated to a point at which no clotting has been observed for periods of observation up to 6 months (figure 5). More than 250 such observations have been made in dogs.

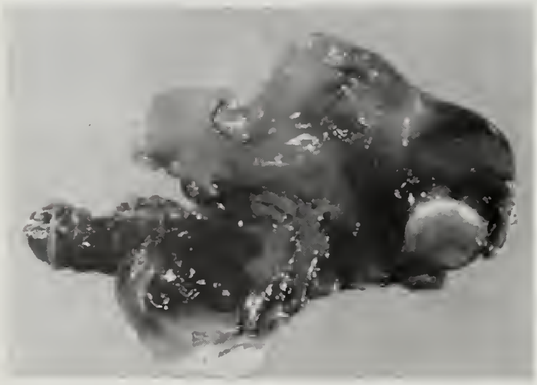
FIG. 4. Uncoated implant after 2 hours in animal.

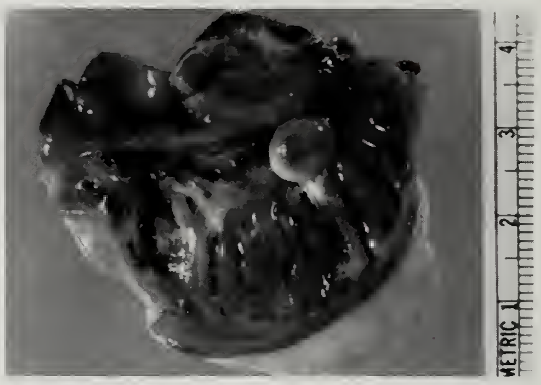

FIG. 5. "Hepacone"-coated implant—6 months after implantation.

As a result of this work we have now coated the cuff of the valvular prosthesis which is used to hold the implant permanently in place with "Hepacone." The entire exposed surface of the cuff is covered with this material (figure 6). Since this method has been used no evidence of embolism has been observed in any patients in whom such an implant has been made. This observation now covers a period of 6 months. In 2 patients in whom autopsy was performed the valve implants have been completely free of any observable clot. The autopsy observations were made at 1-week and 2-week intervals respectively following the implantation. As a result of the experimental and clinical observations there is strong evidence to indicate that the modified discoid prosthesis as it has been currently employed has been the most satisfactory of all of

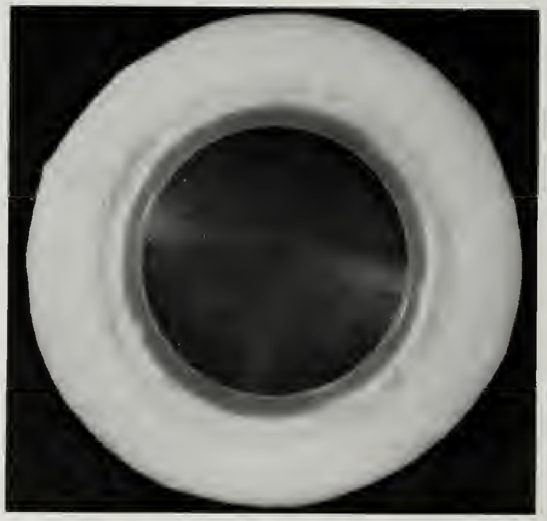
FIG. 6. "Hepacone"-coated valve cuff.

the rigid valve replacements. There has been no evidence of failure of valve function in any of the patients with polypropylene disc valves and in only 1 case evidence of valve failure in all of the modifications of the discoid valve which have been clinically employed since 1963. This experience now covers more than 150 patients.

An additional refinement in the method of valve implantation has further added to the elimination of the problem of clot formation and embolism from valvular prostheses when suture techniques are employed. The customary procedure in the past was to allow the knots of the sutures which hold the prostheses into the valve ring to be exposed on the superior surface of the cuff. This has always appeared to be an undesirable feature even when Teflon-coated surfaces are employed. For this reason 2 methods for the burying of the sutures beneath the cuff have been evolved and utilized. The first of these is illustrated in figure 7. The suture is placed first through the annulus of the valve ring with a double-armed needle. One arm of that needle is then passed through the under surface of the uncoated rim of the valve cuff and is brought back out without penetrating the superior surface. In the aortic valve only 8 to 10 such sutures are usually required for complete fixation. In the mitral valve 12 to 14 such sutures are usually used. After all sutures have been placed in the annulus they are in turn put through the valve cuff. The valve is then gently manipulated into place and the sutures tied.

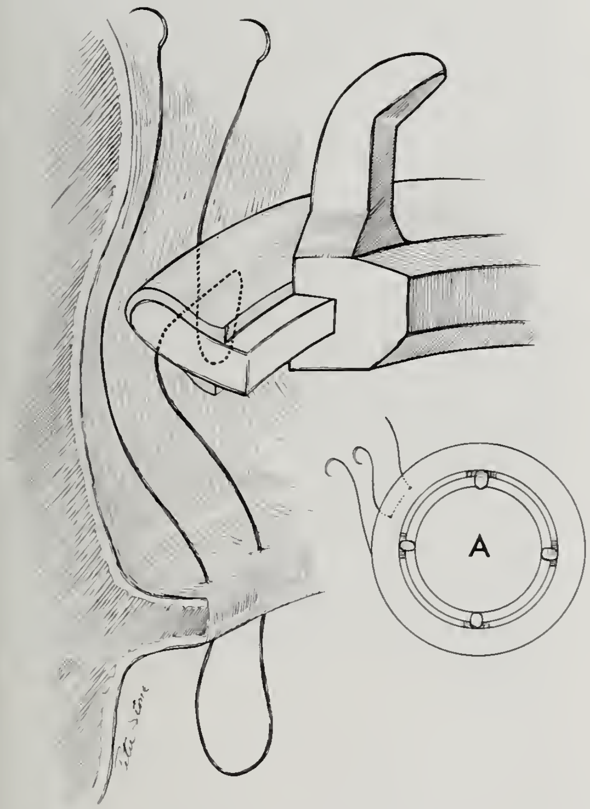

FIG. 7. Suture technique. Note that only 1 arm of suture is passed into cuff but not through the "Hepacone" surface. The knot lies beneath the cuff.

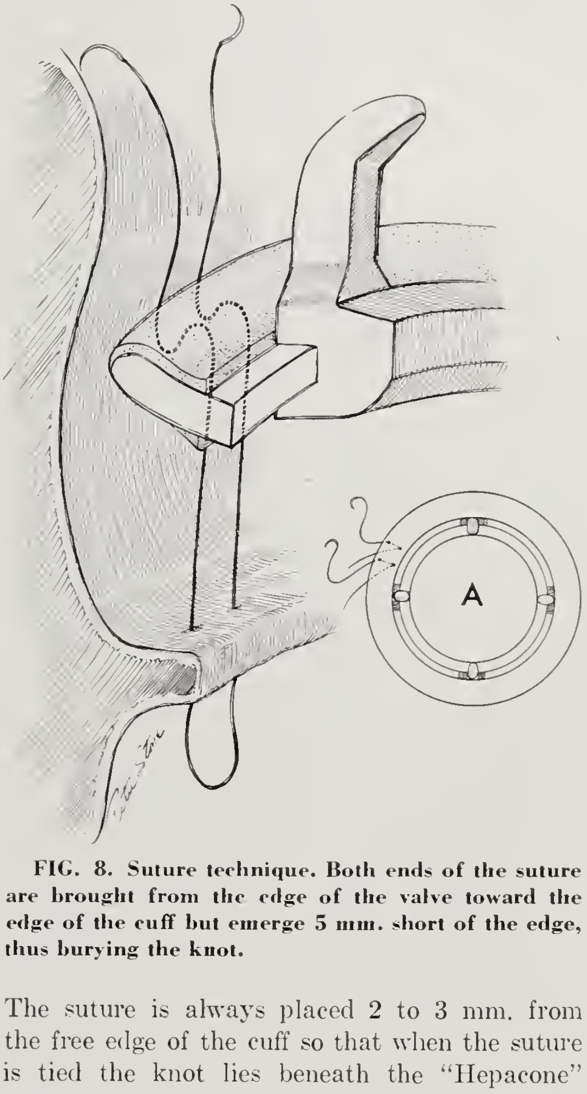

FIG. 8. Suture technique. Both ends of the suture are brought from the edge of the valve toward the edge of the cuff but emerge 5 mm. short of the edge, thus burying the knot.

The suture is always placed 2 to 3 mm. from the free edge of the cuff so that when the suture is tied the knot lies beneath the "Hepacone" portion of the cuff and in contact with the valve annulus in the region where ingrowth of tissue is allowed to take place into the cuff. Thus, no sutures are visible or are directly in contact with the blood stream.

The second method for producing such buried sutures involves again similarly taking the first suture through the annulus with a double-arm needle. Each arm is then brought through the under surface of the valve and toward the edge of the valve from the housing (figure 8). These suture ends are then brought between the proximal arms of the suture, and when they are tied they also lie in the region of the junction of the valve cuff with the body of the valve seat. We have preferred the first method, since it is more rapid and produces essentially the same result.

The great safety of extracorporeal circulation, the great improvements in valve design and resultant decrease in late complications of embolization, the absence of pannus formation, and the negligible incidence of valve failure reveal that it is quite advantageous to operate on patients who are earlier in the course of their disease than has previously been advocated. Almost all of the fatalities associated with replacement of 1, 2, or 3 valves have been associated with the serious changes in the heart muscle, the coronary circulation, or the pulmonary vascular bed which have been produced by the underlying disease process rather than by complications which are intrinsically related to the procedure or to the valvular mechanism. The risk of operation in patients who have not reached the advanced stages of their disease is less than 10 per cent. It would appear advisable, therefore, to offer operation to all patients with serious degrees of aortic stenosis, aortic insufficiency, or combined aortic valvular disease as soon as they show evidence of progression in their asymptomatic state or whenever they show progression in the electrocardiogram to left heart strain and major degrees of left ventricular hypertrophy. Similarly, operation should not be withheld from those patients with serious mitral insufficiency. It is the patient who has already completely exhausted his left ventricular reserve capacity and who has severe evidence of pulmonary hypertension who poses serious problems in the postoperative period.

The postoperative difficulties in the care of the patient with valve replacement is related almost directly to the severity of the disease which the patient demonstrated on admission. Patients operated early in their disease have very few postoperative problems. Those patients with serious impairment of the conduction mechanism, ventricular arrhythmias, intractable heart failure, and extremely large left ventricles associated with or related to pulmonary disease pose major problems in the postoperative care. Such patients must be followed constantly in Intensive Care Units with an experienced team where the control of respiratory function, pO_2, pCO_2, pH, blood volume, electrolytes, coagulation mechanism and renal function can be immediately assayed. Monitoring of the venous pressure, arterial pressure, and cardiac output are also routine. This, however, is no substitute for the skilled judgment of those experienced in the handling of these patients. The information provided by the physiologic data obtained from hour to hour and minute to minute only makes possible the institution of corrective measures before any difficulty would be clinically observable. Without this information therapeutic measures frequently cannot be begun before irreversible changes occur.

The major advances in the treatment of valvular heart disease summarized here make possible the approach to valve replacement with a high degree of safety and a highly satisfactory end-result. It can be anticipated that in properly selected patients an extremely high percentage can be returned to an active and productive life.

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Concepts of the Mechanisms of Tumor Metastasis

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Cancer has 4 biologic mechanisms of spread: by direct extension or invasion of adjacent tissues, by lymphatic dissemination to lymph nodes, by transcoelomic migration, and by hematogenous metastasis in which cancer cells invade the vasculature of the host, embolize, and grow in distant organs. Of these methods the most significant spread is that of hematogenous metastasis. It is axiomatic that the development of distant blood-borne metastatic deposits heralds a lethal outcome for the host.

Until recently the mechanisms or dynamics of cancer-cell metastasis were inadequately studied. The descriptions of metastasis in the literature, although valid and valuable in themselves, were primarily based upon the pathologic anatomy of tumor spread as observed at postmortem examinations. These studies reflected the end-results of a long-standing disease process and furnished little information on the biologic events which led up to this terminal situation. Only recently has attention been directed to what is termed the physiology or dynamics of metastatic growth.

In the classical description of the development of metastasis the primary tumor grows locally during a variable but significant period of time and then encounters blood vessels in its vicinity. The tumor invades the wall of a blood vessel, usually a vein, to establish a neoplastic thrombus. Subsequent dislodgment of this thrombus produces an embolus which is carried to the most proximal capillary network in which it is trapped to develop into a secondary tumor. This concept of neoplastic spread is valid but it oversimplifies the process, for it represents only one, relatively late, type of vascular dissemination.

Phenomena which are not easily explained by this classical description include the development of widespread metastases from a primary tumor which is either not detectable or negligible in size. Conversely, malignant tumors may attain large size without dissemination. Also unexplained are cases in which metastases develop not in the organ of most direct venous drainage, such as the lung or liver, but in another site, distal to these organs. The infrequent occurrence of metastases to muscle, thyroid and spleen has been difficult to understand. Also the establishment of preferential sites of metastases for specific tumors is not well explained by traditional descriptions.

Investigations have recently centered on the study of the dynamic mechanisms of hematogenous metastasis which occur in 3 phases: (1) intravasation, the primary tumor gaining access to the host vasculature, (2) embolization, in which cancer cells are carried to a distant organ, and (3) implantation, in which the neoplastic cells lodge and either survive to produce metastatic cancer or are destroyed. The techniques of investigation of these kinetic processes have included analyses of cancer cells in the circulating blood, in vivo microscopy of tumor cells, time-lapse cinemicrophotography of cancer cells in tissue culture, and the study of the influence of drugs on metastasis.

Intravasation

Intravasation constitutes a critical period in the development of blood-borne spread, because without this first biologic process subsequent phases cannot occur. The propensity of a malignant cell to invade surrounding blood vessels is apparently variable. For example, there is a great difference in the metastatic potential of such skin tumors as basal- and squamous-cell carcinomas and malignant melanomas. This difference is probably related to their capacity for intravasation.

A laboratory model, which is illustrative of the same principle, is the amelanotic (amel) melanoma no. 1 and the amelanotic melanoma no. 3 of the Syrian hamster. These 2 tumor variants are almost identical in histiologic appearance but differ greatly in their biologic behavior. The amel 1 tumor grows to great size locally without ever producing blood-borne metastases. The number 3 tumor metastasizes promptly and widely throughout the animal. In this laboratory the causes of this biologic discrepancy were investigated. When suspensions of cancer cells of these 2 tumors were injected intravenously in hamsters they established metastases with equal frequency. This suggests that a difference in intravasation is the factor responsible for the difference in metastatic potential.[1]

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Recent explanations of neoplastic intravasation begin with the observation that cancer cells possess a decreased cohesiveness for each other which facilitates the separation of these cells from the primary tumor. Studies by Coman,[2] Zeidman,[3] and McCutcheon[4] have established this point by a variety of experimental methods, including agitation of cancer tissue to note the dislodgment of separate cells, and also the direct measurement of the amount of stress required to separate adjacent malignant cells. Further studies by Coman[5] and others[6, 7] indicate that a calcium deficiency of the cell membrane may be responsible for its decreased cohesiveness. Irregularities have been found in the macromolecular structure of cancer-cell membranes by electron microscopy. Yamada[8] and Terayama[9] have also noted a decrease in cancer-cell cohesiveness and have related this to the aggressiveness of malignant growth. An increase in the negative electrical charge on cancer-cell membranes was observed which was inversely proportional to cell cohesiveness.

Decreased cohesiveness allows cancer cells to separate from their tumor of origin, and their motility, which was first observed by Virchow, then becomes operative. Enterline[10] noted that cancer cells were motile at rates up to 4.4 microns per minute. Hirono[11] investigated the motility of ascites hepatoma cells and noted that their motility rates were proportional to their degree of invasiveness.

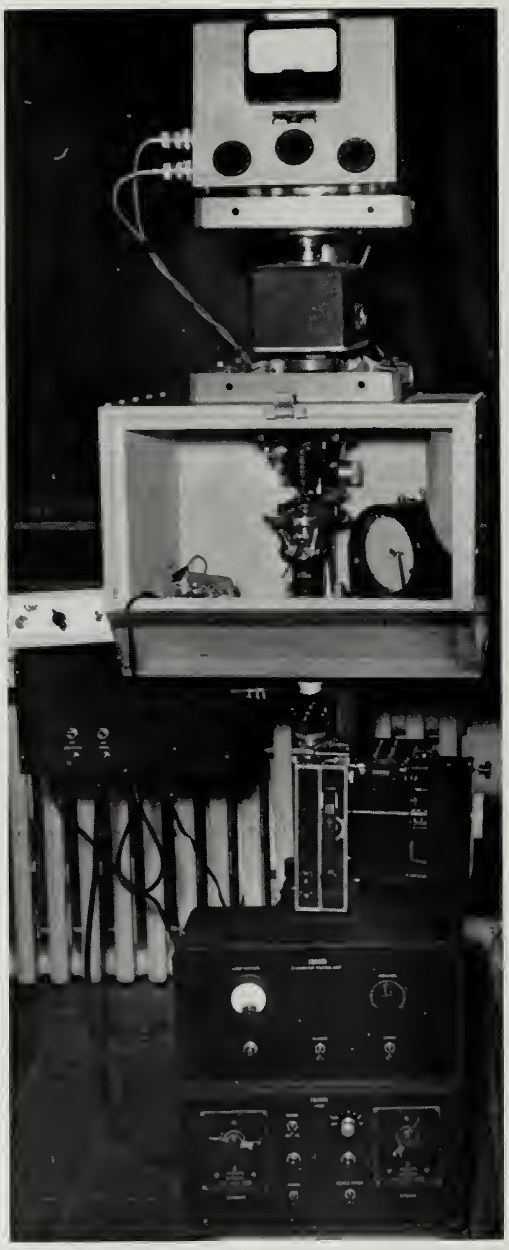

FIG. 1. Apparatus for cinemicrophotographic analysis of cancer cells in tissue culture. Components include (from above downward) photovolt multiplier, lamp, incubator with contained culture and optical system, motion picture camera and drive mechanism, and electric sequencer.

In this laboratory further studies of the amel 1 and 3 tumors were undertaken to determine the causes for their difference in intravasation. These cancer cells were grown in tissue culture and were studied by time-lapse cinemicrophotography (figure 1). The amel 1, or nonmetastasizing cells grew concentrically outward with new growth remaining close to the tumor implant. Many amel 1 cells were not motile and others showed a "Brownian," or to-and-fro motion. These cells had a tendency to cohere and clump. Cell velocity varied between 0 and 6 microns with an average velocity of 1.9 microns per minute. The amel 3 or metastasizing cell, in addition to concentric outward growth, showed cellular proliferation radiating in a linear manner away from the explant. Rate of growth was rapid and aggressive. The cells did not cohere but were characteristically separate. The vast majority of cells were actively motile, and their velocity of ameboid motility varied between 1 and 8.5 microns per minute. Many more of the cells were motile than with the amel 1. Average velocity was 6.1 microns per minute. Ameboid motility moved these cells in a specific direction rather than establishing a back-and-forth motion. It is concluded that the amel 1 and 3 tumors differ in their capacity to metastasize because of their differences in cohesiveness and motility.[12]

Other factors which may be responsible for allowing passage of a cancer cell into a venule include the capacity for transendothelial migration by the cancer cell, anatomic disruption of the venule, elevated intratumor pressure, and the Venturi effect of blood flow.

Embolization

Embolization is the process whereby a neoplastic cell is carried to a distant site. Methods of detecting cancer cells in the blood have been developed by Pool and Dunlop,[13] Engell,[14] Moore,[15] Potter,[16] and others. Interpretation of these reports indicates that cancer cells may be present in the blood in very "early" stages of cancer, and that their number increases with the duration of the tumor. Manipulation of a tumor produces showers of malignant cells into the venous blood. Fortunately, not all of these cells will produce metastatic foci, since the vast majority of malignant cells are destroyed or contained by the host organism. This fact has been demonstrated in experimental animals in which at least 95 per cent of embolizing cells are destroyed. In some species 600,000 cancer cells must be injected to produce a single metastasis. In the clinic many patients who are positive for circulating cancer cells do not develop metastases in extended periods of follow-up.

Implantation

Implantation is the process wherein a cancer cell is arrested in a vascular network and grows through an endothelial surface to become established in the stroma. Two theories have been advanced to explain the sites of these metastases. The mechanical theory states that anatomic factors are responsible and that a tumor metastasizes to the organ to which its venous drainage is directed ("seed theory"). This hypothesis maintains that no parenchymatous organ is more adaptable than others to the growth of embolic tumor cells. The second or selective affinity theory holds that specific organs are uniquely receptive to the growth of specific tumors ("suitable soil"). Neither of these theories alone explains all the phenomena of tumor implantation.

It was formerly believed that a cancer cell would be trapped by the first capillary network to which it was delivered because the average size of a cancer cell exceeds the histiologically determined diameter of a capillary. It was, therefore, difficult to understand the development of metastases distal to this draining capillary network. Recent in vivo studies of capillary circulations, however, suggest that the microcirculation has an enormous capacity for the passage of single malignant cells or neoplastic clumps of cells vastly larger than the capillary. In vivo study (figure 2) of the microcirculation of the hamster cheek pouch[17] shows that amelanotic melanoma cells passed promptly through these capillary networks by either distention of the capillary or by the opening of arteriolar-venular shunts.

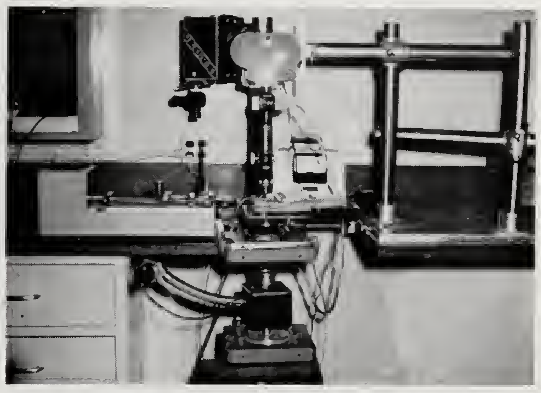

FIG. 2. Apparatus for microscopic observation of embolization of cancer cells to the inverted cheek pouch of the anesthesized hamster. High speed motor-driven motion picture camera is in place above the optical tube which is positioned over the cheek pouch. At left is microfusion pump for quantitated delivery of melanoma cells.

The interreaction between a cancer cell and a capillary network is apparently specific and variable. For example, in the rabbit the Brown-Pearce carcinoma produces metastases distal to the lung in 90 per cent of specimens. The VX2 rabbit carcinoma metastasizes to the lung but very rarely beyond it. The size of the cancer cell is not the responsible factor, because the Brown-Pearce carcinoma is 20 per cent larger than the VX2 tumor cell. In vivo study of the microcirculation of the rabbit lung[18, 19] indicates that when suspensions of the 2 tumor cells are injected via a catheter in the pulmonary artery the VX2 tumor emboli arrest the microcirculation of the lung. This circulatory arrest is responsible for the development of the VX2 metastatic tumors. Brown-Pearce carcinoma cells similarly injected pass immediately through the lung field without arrest in the circulation and metastasize to distal organs. Apparently specific differences in the interaction between the cell membranes of these cancer cells and the microcirculation of the organ play a significant role in determining whether tumor cells will be arrested and grow to produce metastases.

Other research data suggest that metastases develop when tumor-cell emboli are arrested in capillaries. It is hypothesized that metastases are not commonly found in organs such as muscle, thyroid or spleen because tumor-cell emboli are arrested in the arterioles of these organs or are shunted out of the organ rather than lodging in the capillary.

Other factors operative in determining the success or failure of disseminated cancer cells to grow have been studied by Wood,[20] who demonstrated that cortisone increases the number of metastatic tumors in experimental animals. He noted that such factors as pregnancy, stress, and steroids enhance the development of metastatic growth while anticoagulants such as heparin and Dicumarol® or fibrinolitic agents decrease the number of metastatic deposits.

Summary

Recent studies of the mechanisms of metastases by means of new investigational methods suggest that this process begins soon after the development of the primary tumor. Decreased cohesiveness and ameboid motility of malignant cells allow their early entrance into the host vasculature. The great majority of these cells are destroyed, or their growth is prevented by the host. Lodging of tumor cells in capillaries, which occurs in periods of temporary arrest of the microcirculation, favors the growth of metastatic tumors. Pharmacologic agents play a modifying role in the development of metastases.

No change in the clinical management of cancer patients is warranted at present on the basis of these studies, but it is hoped that, in the future, greater knowledge of the mechanisms of metastatic growth will improve the control of this ominous characteristic of cancer.

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Effect of Contralateral Nephrectomy and Renal Nerves on Renal Function*

ROGER BAKER, M.D., PH.D.† AND EDWARD TARABULCY, M.D.‡

As far back as 1840 Pappenheim[1] showed that autonomic nerve fibers enter the kidneys together with the renal arteries and run along these arteries down to their finest branches. Do these renal nerves have any effect on renal function? If so, what is that effect? This has been the subject of much controversy since 1869 when Beale[2] described nerve filaments distributed to the renal tubules. The present experimental work was undertaken with a view toward trying to further our knowledge in this still unsettled subject.

Materials and Methods

The experiments in the present study were carried out on 21 male and female dogs. One ureter was surgically diverted from the urinary bladder. This permitted baseline studies made upon bladder urine to represent function of 1, rather than both kidneys. After the dogs had fully recovered from the operation renal function studies were carried out prior to and after excision of the kidney having ureteral diversion.

To study the influence, if any, of nerves on renal function, it was decided to denervate the remaining kidney by cleaning all tissues from the renal artery, renal vein and ureter for a distance of 2 cm. These vessels and ureter were stripped clean down to adventitia. In order to ensure total denervation the solitary kidney was then excised by complete transection of the renal artery, vein and ureter. The kidney was next replaced in its bed and the ureter and blood vessels reanastomosed. Renal function studies were again performed and repeated monthly over a period of 10 to 12 months. All electrolyte and renal function determinations were made on unanesthetized dogs and after hormonal effects of surgery on renal function had subsided.

Results

Numerous parameters of renal function were investigated in addition to corrected urea clearance, urine and serum chloride, serum sodium and potassium, intake, output and specific gravity. Because of the usual laboratory problems associated with multiple collection of urine samples from dogs over long periods of time, many of these determinations were not considered valid and are not reported.

The effect upon renal function of contralateral nephrectomy is presented in figures 1 through 4. There is no significant immediate or delayed change in corrected urea clearance, serum sodium and serum potassium after contralateral nephrectomy. Fluid intake and volume of urine output were also unchanged. Although serum chloride remained within normal range, urine chloride output increased until the 18th to 20th day after contralateral nephrectomy, when it reversed to normal. The urine specific gravity was depressed until the 24th to 28th day, when it returned to the preoperative level.

The effect upon renal function of total denervation of the solitary kidney, i.e., autotransplantation, is presented in the same figures 1 through 4. Within the first 42 days after denervation, urea clearance, serum sodium, potassium and chloride remained normal while specific gravity decreased and urine volume increased. Chloride loss in the urine remained increased until 30 to 60 days following autotransplantation.

Follow-up studies revealed all determinations to be normal in 6 dogs that were studied for 10 to 12 months postdenervation (autotransplantation). In 3 other dogs all parameters of study were also normal except for a persistent increase in chloride loss in the urine. The mean

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data of these results are presented in figure 4. The difference observed in urinary chloride concentrations in the 2 groups could not be resolved or accounted for by intravenous pyelography, histologic examination of the renal parenchyma, or difference in nerve regeneration on the adventitia of the reanastomosed renal arteries.

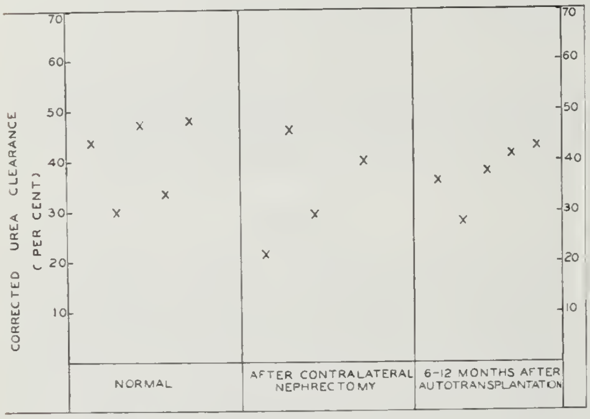

FIG. 1. Mean determinations of urea clearance after contralateral nephrectomy and also after total denervation of the solitary kidney indicating no change in urea clearance.

Discussion

A number of investigators have studied the effect on renal function of splanchnicectomy and/or excision of nerves of the renal pedicle. They obtained conflicting results and there is controversy relative to their conclusions. For example, some believe renal function is independent of the nervous system and that any change in urinary output secondary to nerve impulses is due to changes in renal blood flow. Some investigators found altered renal function in the anesthetized but not the unanesthetized animal. This effect of anesthesia can be related to increased vasomotor tone in the innervated kidney, leaving a greater blood flow in the denervated organ. Some investigators have noted diuresis unrelated to alterations in renal blood flow. Meilman,[3] Blake,[4] and Thompson[5] reported an increase in excretion of sodium (with or without increase in water output) that was not observed in the experiments reported in this paper.

In many of the experiments reported earlier there is variability in degree of renal denervation which can account for differences in the results obtained. In the case of splanchnicectomy this represents only one source of renal denervation. In those experiments in which excision of the nerves on the renal artery and vein is done, variable degrees of renal denervation can be obtained. Nerve fibers are also found in the substance of the adventitia and even the media of the renal artery and its branches. Complete renal denervation can be achieved only by severing the entire renal pedicle and ureter and then reanastomosing the renal artery, vein and ureter. After this type of total denervation (autotransplantation) we observed only minimal and transitory changes in renal function that reverted to normal in a maximum of 60 days. Other workers using identical or similar methods of effecting total renal denervation have obtained comparable results. Maluf,[6] Unik,[7] Tischler,[8] Dempster,[9] and Zaretzky,[10] and their respective co-workers, found transient and not permanent change in renal function after total denervation. The last named author observed that with water loading, diuresis remained unstable at the end of 3 months.

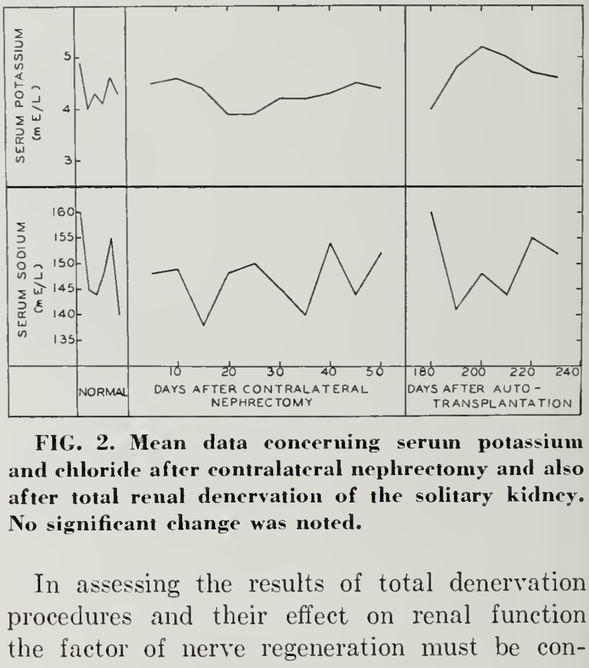

FIG. 2. Mean data concerning serum potassium and chloride after contralateral nephrectomy and also after total renal denervation of the solitary kidney. No significant change was noted.

In assessing the results of total denervation procedures and their effect on renal function the factor of nerve regeneration must be considered. This was first brought to light by Dogliotti.[11] He demonstrated regeneration of the renal nerves following their division in dogs. There was no evidence of regeneration in the first month following denervation. There was partial regeneration in 40 to 60 days and complete regeneration by 4 to 7 months. Zaretzky[10] and also Couch[12] observed some nerve regeneration in the hilum of canine renal autografts or autotransplanted kidneys at 1½ to 3 months. Regeneration was complete by 6 months.

It can be concluded that no nerve regeneration occurs prior to 6 to 7 weeks after denervation. Within 3 weeks after denervation, i.e., prior to nerve regeneration, our dogs had normal urea clearance, serum sodium, potassium and chloride. They still had a mild diuresis associated with lowering of specific gravity and some increased chloride loss. Glomerular filtration, renal blood-flow, and tubular secretion and reabsorption were normal within 3 weeks of denervation and hence prior to nerve regeneration.[8]

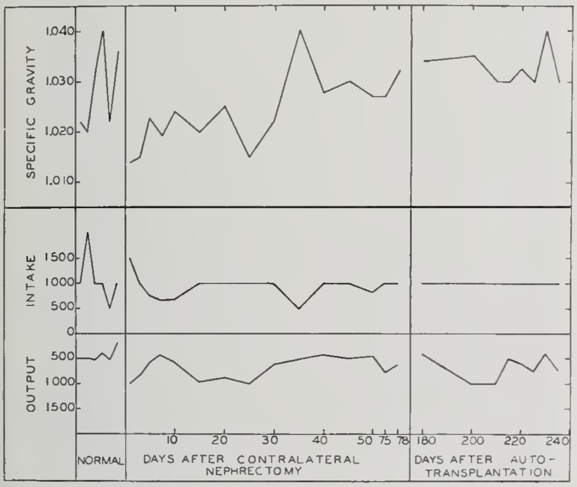

FIG. 3. Mean data concerning urine specific gravity, fluid intake, and urine output after contralateral nephrectomy and also after total renal denervation of a solitary kidney. Note drop in specific gravity after contralateral nephrectomy.

Excision of 1 kidney in a dog results in comparable alteration in function of the opposite kidney, as in denervation of a solitary kidney, i.e., transient diuresis, lowering of specific gravity, and increased urine chloride.

Summary

The data presented in this paper and that of others using similar techniques for total denervation indicate minimal abnormalities of renal function within the first 20 to 60 days postoperatively. These changes in function are minor and in no way endanger survival of the dogs in our series or those studied by others. The fact that these changes in function revert to normal within 20 to 60 days of autotransplantation can be accounted for by nerve regeneration about the renal artery, although this is unproven. Even if no regeneration of renal nerves occurred, the alteration of renal function associated with denervation is of little importance. In the dog there is no evidence to indicate that renal nerve-supply plays a significant role in normal renal function. Based on the parameters of study used similar minor tubular alterations are produced in nondenervated kidneys when contralateral nephrectomy is performed.

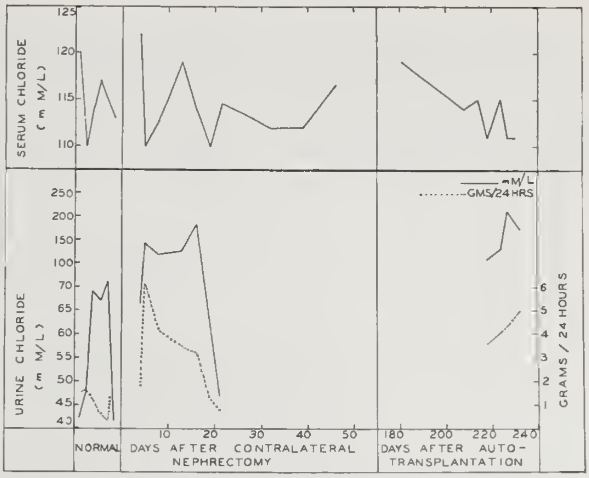

FIG. 4. Mean data relating to serum chloride and urine chloride after contralateral nephrectomy and also after total renal denervation of a solitary kidney. Note increased loss of chloride in urine.

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Comments on Experimental Surgical Techniques for Cerebral Aneurysms and A-V Malformations

ALFRED J. LUESSENHOP, M.D.*

DESPITE RECENT TECHNICAL ADVANCES major problems in the surgical management of bleeding cerebral aneurysms and arteriovenous malformations remain unsolved. Hypothermic anesthesia, osmotic dehydrating agents, and hyperventilation anesthesia have improved the surgical treatment, but the most recent assessment of the overall problem indicates that surgery, either by a direct approach or ligation of cervical arteries, remains essentially a prophylactic maneuver, useful for preventing delayed recurrent hemorrhage but offering little during the critical period of active or recurrent bleeding.

This is most striking when one analyzes the results of surgery for aneurysm in patients at varying periods following the initial hemorrhage. In those who have recovered completely from their hemorrhage surgical repair or obliteration of the aneurysm is accomplished with a mortality below 5 per cent. However, with progressively greater degrees of increased intracranial pressure, neurological deficits, and bloody cerebrospinal fluid, the operative mortality and morbidity rapidly climb, ultimately reaching 100 per cent in patients with extreme degrees of increased pressure. Therefore, the goal of surgical management has been proper timing for the intervention to allow restoration of the patient to the most favorable clinical status. To achieve this optimal time for surgery many patients may succumb to recurrent bleeding while others never reach satisfactory clinical status.

These problems have led to the investigation of alternate techniques which might obviate direct exposure of the aneurysm by craniotomy and hence not be limited by the clinical status of the patient. Two such techniques, currently being pursued, are the stereotactic and the intra-arterial. The former is essentially the introduction and guiding of an electrode by radiological control to the vicinity of the aneurysm to electrically induce thrombosis with a direct current applied over several hours.[1] Although of comparative technical simplicity, the method is, to date, limited by the necessity of penetrating the delicate aneurysmal wall with the thin wire electrode and a tendency for the aneurysm to recanalize by gradual dissolution of the induced thrombosis. The method has reached clinical trial and with further modification may become useful for dealing with some aneurysms.

For the intra-arterial approach a technique for catheterization of the proximal intracranial arteries has been developed and also has reached limited clinical trial.[2] Various types of catheter tips may be used to occlude the intraluminal orifice of the aneurysm. Future development of this may be limited by the spasm of the parent artery which frequently accompanies saccular aneurysms during the acute phase of bleeding. However, certain aneurysms are so anatomically situated that artificial emboli of predetermined size and shape may be introduced into the appropriate cervical artery and by the anatomic characteristics of the aneurysm and associated hemodynamics occlude the intraluminal orifice of the aneurysm without seriously interfering with the normal surrounding circulation. Some inoperable aneurysms at the terminus of the basilar artery or at the division of the middle cerebral artery may be suitable for this. An example is shown in figures 1, 2 and 3. This aneurysm at the end of the middle cerebral artery represents a blind pouch; the adjacent normal branches had spontaneously thrombosed. Emboli too large to fit into the normal arteries were introduced, ultimately occluding the aneurysm.

In general, however, to treat the majority of the aneurysms by this technique methods of external control, such as magnetic fields, or emboli controlled by ligatures will be necessary. One such modification has been the use of minute iron particles (carbonyl iron suspension) injected into the carotid circulation and drawn into the aneurysm sac by a probe magnet stereotactically positioned at the dome of the aneurysm.[3] This also has had limited clinical trial.

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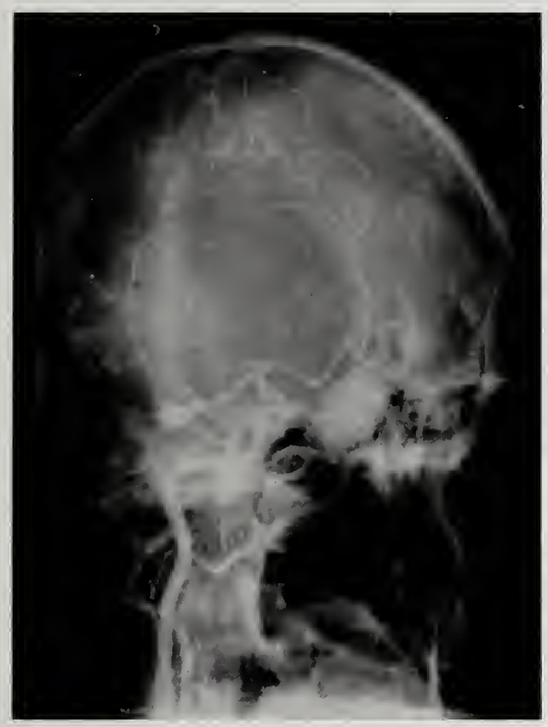

FIG. 1. Oblique arteriogram showing an aneurysm at the end of the middle cerebral artery. The Sylvian arteries are thrombosed.

All these methods, although in a primitive stage of development, offer a possibility of eliminating the aneurysm irrespective of the clinical status of the patient and therefore are not subjected to the restrictions of timing heretofore necessary.

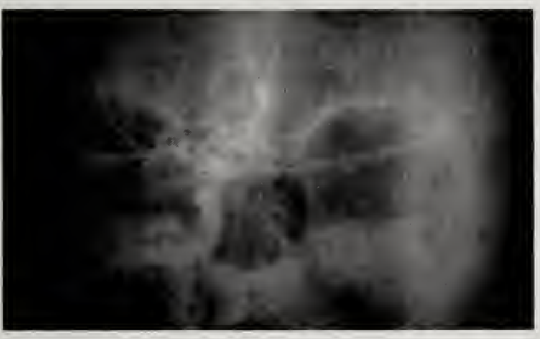

FIG. 2. Two 2.5 mm. emboli arrested in the aneurysmal sac.

Arteriovenous malformations of the brain are considerably heterogenous with anatomic characteristics ranging from minute artery to vein shunts to enormous vascular abnormalities involving the entire cerebral hemisphere, the dural covering, the bone, and the scalp. All have the potential of spontaneous bleeding or, by gradual enlargement, the production of a progressive neurologic deficit. Although smaller lesions in relatively silent areas may be excised without difficulty, a great number are so situated that direct excision is not feasible. Certain anatomic characteristics of this latter group make an intra-arterial approach practical. Because of increased blood flow the feeding arteries become greatly enlarged and may appear as direct arterial channels leading from the cervical arteries. The arteries to normal brain remain of normal size. Therefore, emboli too large to fit into the normal branches may be introduced into the cervical arteries and become arrested at the vascular origin of the malformation.

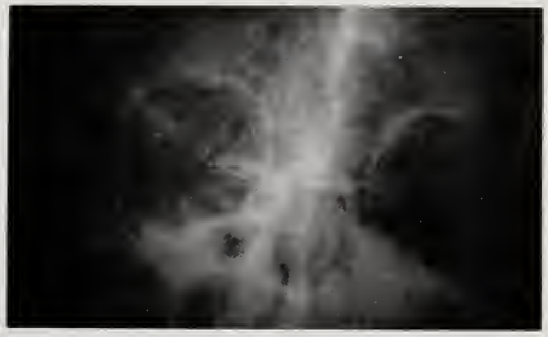

FIG. 3. The third 2.5 mm. embolus occludes the neck of the aneurysm.

The technique of artificial embolization has been useful in the management of some large, heretofore inoperable lesions.[4, 5] Although complete anatomic elimination of the lesion has not been uniformly achieved, certain malformations may be so reduced in size that direct incision thereafter becomes a relatively simple matter. An example of this is shown in figure 4. This lesion, situated in the right anterior temporal lobe and insula, has been considerably reduced in size by a single embolus blocking the main trunk of the temporal polar and anterior temporal arteries. Chances of direct surgical incision are considerably enhanced.

Summary

The present status of surgical management of cerebrovascular abnormalities indicates the need for methods of eliminating the potential for recurrent bleeding that are not restricted by the clinical status of the patient. The experimental

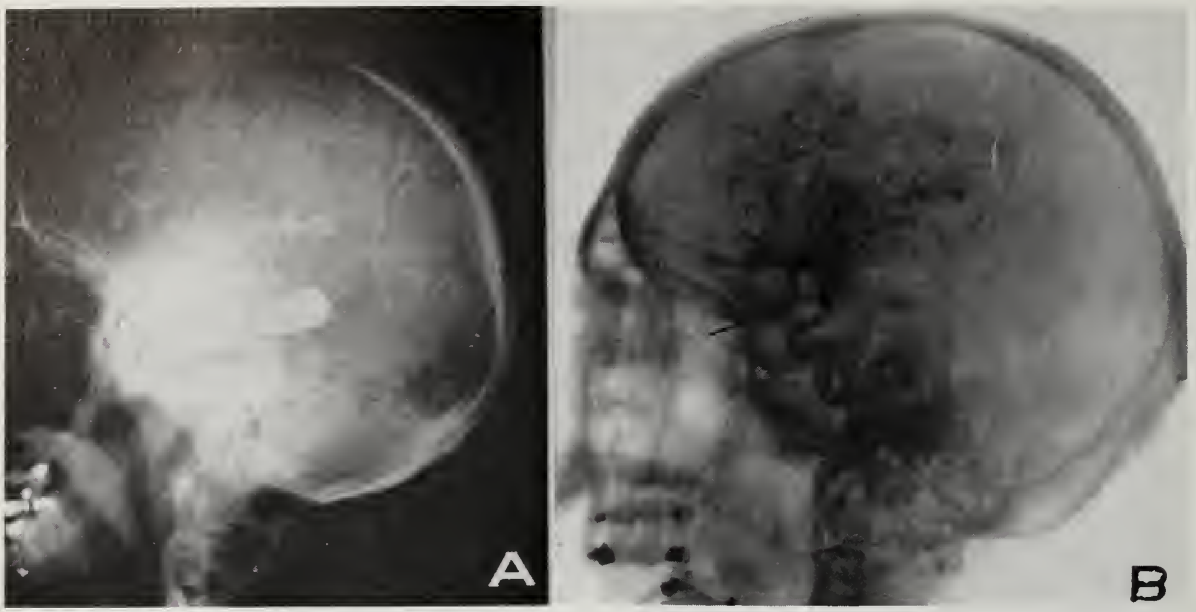

FIG. 4. An arteriovenous malformation of the temporal lobe, preoperative (left) and following introduction of a single 3.0 mm. embolus indicated by arrow (right).

methods of an intra-arterial approach and a stereotactic approach have been described.

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Importance of Sodium-Containing Crystalloid Solutions in Hemorrhagic Shock*†

JOHN S. DILLON, M.D.‡

FOLLOWING SIGNIFICANT HEMORRHAGE and most especially when this hemorrhage results in shock, restoration of circulating volume is of foremost importance. A variety of solutions are available for intravenous infusion to correct hypovolemia. Those most commonly used in this country include homologous whole-blood transfusions, plasma, or plasma derivatives such as albumin, or colloid solutions such as dextran. Accepted surgical and physiologic principles have long indicated that effective blood-volume replacement depends on the presence of molecules in the infusion of sufficient size that they do not readily diffuse through the capillary membrane and thus remain within the circulation for a prolonged time. These maintain plasma volume by "colloid osmotic effect," a concept originating with the work of Starling[1] in the last century.

Crystalloid solutions, on the other hand, because they readily pass through the capillary membrane are considered to maintain or restore circulating volume only transiently and inadequately. Ebert and Stead[2] have shown that when a liter of blood is removed from human volunteers an equivalent volume of saline fails to restore circulating volume. Others[3] have shown that colloid solutions correct experimental shock due to hemorrhage more effectively than saline when saline is used in equivalent volumes. A number of studies, however, question the superiority of colloids, and in the past several years much evidence has risen supporting the contention that a properly selected crystalloid solution, a buffered salt solution, has real value in the treatment of hemorrhagic hypovolemia and shock.

Schwarz[4] in 1881 first demonstrated that dogs subjected to shock by acute hemorrhage could be salvaged with the use of a buffered saline infusion. In 1946 Sayers et al[5] demonstrated that rodents subjected to acute hemorrhage survived as frequently when given normal saline as when treated with whole blood. Significantly, Sayers' favorable results were obtained when 2.3 to 3.9 times larger volumes of saline were used than that of blood. Rosenthal[6] confirmed this work. Saline used in larger quantities than blood achieved survival rates equal to that of blood in hemorrhagic shock in rats.

A number of investigators have employed a standardized canine shock preparation in studies employing saline. Each has been a modification of Wiggers' irreversible shock preparation[7] in which blood is allowed to flow into a chamber to produce a reduction in arterial pressure which is then maintained for a period of time.

Stirman[8] treated 20 dogs placed in shock by this method. Two of 10 dogs treated by returning the blood survived. In the other 10, lactated Ringer's solution (in a volume equal to 25 per cent of the extracellular fluid) was infused prior to returning the blood. Six of these survived. Shires et al[9] maintained a series of dogs in shock for 90 minutes at 50 mm. Hg and 45 minutes at 30 mm. Hg mean arterial pressure using Wiggers' technique. Of 10 dogs treated by returning the blood only 2 survived. Lactated Ringer's solution given prior to the blood (in a volume equal to 5 per cent of the body weight) increased survival in 7 of 10 dogs. When plasma was substituted for the salt solution only 3 of 10 dogs survived.

Wolfman et al[10] varied the shock preparation to include an element of trauma. The mean arterial pressure was brought to 50 mm. Hg and maintained for 1 hour by bleeding into a reservoir. Celiotomy was then performed and the intestines manipulated to produce a pressure of 30 mm. Hg which was maintained for 1 more hour. Dogs treated by returning the removed blood had a fatality rate of 80 per cent. Use of additional homologous blood (in a volume equal

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to 25 per cent of the calculated extracellular fluid volume) resulted in a mortality of 90 per cent. Introduction of lactated Ringer's solution in a volume equal to 25 per cent of the calculated extracellular fluid volume prior to returning the blood reduced the mortality to 20 per cent. The use of a nonelectrolyte solution (5 per cent dextrose in water) rather than lactated Ringer's prior to infusing the blood had no such beneficial effect.

Dillon et al[11] have used larger quantities of lactated Ringer's solution and less blood with equally good results. Dogs were placed in shock at 70 mm. Hg mean arterial pressure for 90 minutes, then 30 mm. Hg for 60 minutes. Fifty per cent of 24 dogs treated by returning the blood survived. Hartmann's lactated Ringer's solution buffered to pH 8.5 gave equally good results, 10 of 20 dogs surviving. The volume used was calculated as the volume of plasma removed plus 4.3 times the volume of red blood cells removed during the hemorrhage, or about 2½ times the volume of blood. When this volume of buffered saline was followed by half the blood removed survival rose from 50 to 87 per cent. Substitution of an equivalent volume of 5 per cent dextrose in water followed by half the shed blood resulted in only 14 per cent survival. Use of clinical grade dextran (mol. wgt. = 70,000) in fructose prior to the reinfusion of blood resulted in survival in 25 per cent of the dogs.

At the Surgical Metabolic Research Laboratory at Georgetown University an identical shock preparation has been used. Over 90 per cent of dogs treated by returning the blood removed died (table 1). Use of Rheomacrodex® (10 per cent in saline) in a volume equal to the shed blood alone or in combination with replacement of half the shed blood has resulted in no survivals. Survival at the same time with Hartmann's solution in the same quantity as described above followed by half the blood shed occurred in over 90 per cent of the animals.

In each of the above experiments sizable quantities of salt solution used prior to blood transfusion have shown definite therapeutic advantage over blood alone or in combination with colloid solutions or nonelectrolyte solutions. The reason for this advantage is under active investigation.

The use of blood, blood and plasma, or buffered saline with blood in Shires' experiments resulted in blood volumes following treatment equal to or greater than the normal preshock volume. In our experiments at Georgetown the same was true of blood or combinations of half the shed blood with low molecular weight dextran or lactated Ringer's solution in the volumes mentioned above. It seems obvious that the beneficial effects of the sodium-containing solutions do not reside in improved intravascular volume replacement.

A number of possible explanations are apparent. Use of buffered salt solutions results in a lowered hematocrit and consequently may improve flow through capillaries. While earlier workers using rodents have employed normal saline, the most recent experiments have used solutions containing lactate. Some possible beneficial effect may arise from correction of the acidosis of shock by metabolism of lactate. Experiments are under way to ascertain the role this may play.

TABLE 1: Mortality by Method of Treating Controlled Hemorrhagic Shock in Dogs by Modified Wiggers' Preparation

Treatment No.	Method of Treatment	No. Dogs	No. Died	No. Lived	Proportion Surviving
1	Blood removed	11	10	1	0.09
2	Lactated Ringer's solution, pH 8.7 (per formula) and ½ blood removed	12	1	11	0.92
3	Low molecular-weight dextran (M.W. 40,000) (volume = blood removed)	5	5	0	0.00
4	Low molecular-weight dextran (volume = blood removed) + ½ blood removed	5	5	0	0.00

The most likely answer, however, probably rests in the propensity for noncolloid sodium-containing solutions to distribute throughout the extracellular space, not just within the vascular space.

The status of the entire extracellular fluid and functional sodium mass in shock is of interest. Shires[9] has shown a loss of extracellular fluid during shock in excess of that explained by the removal of plasma in shed blood. Infusion of blood or plasma with blood fails to replace this deficit. Use of lactated Ringer's solution preceding the blood does.

Dillon et al[11] have shown a residual deficit of functioning sodium mass in animals treated by blood alone approximating 8 mEq. per Kg. of body weight. This is based on urinary sodium excretion under sodium load. Subsequent work in this laboratory with S35 and Na22 dilution techniques confirms not only a disparate loss of functional sodium mass in excess of sodium removed in the blood during shock but successful replacement with Hartmann's solution plus blood, though not when blood alone is used.

Sodium mass deficits of 17 mEq. per Kg. or greater are frequently seen in hemorrhagic shock with these techniques. The deficit, attributable to sodium removed in plasma during hemorrhage, is in the order of only 2 to 4 mEq. per Kg. Returning this sodium by reinfusing blood still results in a sodium deficit of 8 mEq. or more per Kg.[12]

The significance of deficiencies in functional corporal sodium mass of this magnitude in otherwise normal mammals has been discussed by Grayson et al[13] and by Elkinton and Danowski.[14] Certainly acute deficits are poorly tolerated and animals recently placed in shock should be even more susceptible to their deleterious effects.

Since these deficits are corrected by the use of large quantities of Hartmann's solution and a marked improvement in survival is seen concomitantly, it seems reasonable that irreversibility in hemorrhagic shock is at least partly related to acute functional sodium deficits.

Summary

Use of lactated Ringer's solution prior to infusing blood is superior to blood alone or in combination with colloid or nonelectrolyte solutions in experimental irreversible hemorrhagic shock. This is probably due to restoration of functional sodium mass not otherwise replaced. The concept of hemorrhagic shock as a condition due solely to inadequate volumes of circulating fluid seems no longer tenable. Extravascular sodium metabolism is of great importance in hemorrhagic shock.

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Diagnosis and Conservative Treatment of Ordinary Low Back Pain

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One of the most common complaints relating to the musculoskeletal system which patients present to the generalist is that of low back pain. The success or failure of the treatment depends on a number of factors. Foremost among these are the various mechanical factors which influence the lumbosacral spine, the differential diagnosis, the evaluation of the needs of the patient, and the various suitable forms of treatment. All of these factors must be coordinated in the mind of the physician who hopes to alleviate this most troublesome and disabling symptom-complex. It might be added that a sense of confidence and enthusiasm on the part of the physician will be transmitted to the patient who often is discouraged and depressed when the nature of his complaint is chronic. If the physician lacks an active interest and understanding of the etiology and pathomechanics of the disability and is unwilling to undertake with his patient a concentrated program of correction and prevention he is doomed to failure. The natural healing processes may still be self-corrective but usually result in an unduly long and painful period of disability. This presentation will be limited to the lower part of the back. While there are many causes for low back pain only the most common entities will be presented here.

Postural Low Back Pain

The majority of cases can be explained on a postural basis. Posture is an important factor not only in the static sense such as in sitting, standing, and lying but also in the dynamic positioning of the body. Additional strains may be placed on the female back by pregnancy and the burden of house work and child care. Obesity may play an important role in the early initiation of disc degeneration and osteoarthritis. It complicates treatment and delays recovery. Improper beds, chairs, and especially shoes are also factors. The common denominators frequently seen are weak muscles and poor patterns of physical activity. This is not usually seen in persons who are well conditioned in the occupation or activity they practice and who use their backs every day. Most backache is primarily a product of abuse or of soft muscles and a soft life.[1]

Good posture can best be determined by examining the patient from the side. The head should be in the mid-position with the chin drawn in and down, so that the lobe of the ear points to the shoulder. The tip of the acromion should be in line with the tip of the ear. Neither the head nor the abdomen should be allowed to protrude. The shoulders should be level and not rounded forward, with the buttocks pulled under rather than protruding from behind. The weight should be balanced toward the center of the knees and at the outer border of the feet so that a plumb line would fall midway between the ball and the heel and toward the outer edge of the foot (figure 1).[2]

Faulty posture can be corrected by proper training and suitable exercises. The basic principle of good standing posture is balance between the lower extremities and alignment of the vertebrae. If there is exaggeration of the lumbar lordosis with relaxation of the abdominal musculature it is important to stress back flattening. The key to this exercise is to increase the strength of the abdominal muscles and gluteus maximus while stretching out the tight, contracted hamstrings and tight erector spinae.

The degree of increased lumbar lordosis has a direct effect on the angle of inclination from the horizontal at the lumbosacral junction. As lordosis increases, the lumbosacral angle also increases, causing greater shearing forces to act on the structures in this area. It therefore becomes apparent that if the lumbosacral angle is decreased by means of muscle strengthening and stretching exercises, the shearing stress will be reduced and pressure on the supporting structures will be relieved. In order to decrease the lumbosacral angle the muscles which flex the spine must come into play. The pelvis must be rotated forward so that the column of the lumbar vertebrae is supported in a more vertical axis resting on the sacrum as a base.

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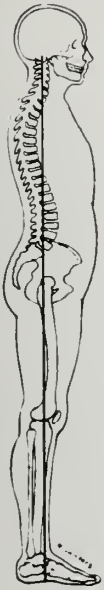


FIG. 1. Center of gravity in the vertical weight-bearing position. The center of gravity falls posterior to the vertebral bodies in both the cervical and lumbar regions and anterior to them in the dorsal region. Sketch shows relationship of a plumb line to various skeletal landmarks in correct posture. Reproduced by permission from Williams.[3]

It is necessary, then, to consider the muscles which act to flex and extend the spine. The most powerful group, the erector spinae, extends the spine and has enabled man to attain the upright position. This, however, forced the lumbar vertebrae into a position of lordosis. Other muscles which are less obviously extensors of the spine are the sartorius, rectus femoris, and tensor fasciae latae. In the erect position and with the knee joint fixed, their contraction causes a downward dip of the pelvis, thereby increasing lumbar lordosis and the lumbosacral angle. Acting in opposition to the extensors of the spine are the anti-antigravity muscles, if they may be called that, since their action is antagonistic to the antigravity muscles. These are the muscles of the anterior abdominal wall, the gluteus maximus, and the hamstrings. Contraction of the rectus abdominus causes a cephalad movement of the symphysis pubis, rotating the pelvis under the column of vertebrae (figure 2).

The gluteus maximus performs the same function, tilting the posterior portion of the pelvis caudad with the femur fixed. The hamstrings act in a similar fashion when the knee is fixed. The iliopsoas produces extension of the spine since its origin lies posterior to the vertical axis. Treatment should be directed toward reducing lumbosacral extension, thus shifting the center of gravity forward and relieving the posterior pressure at this site. In order to accomplish this it is necessary to actively develop the flexors of the lumbosacral spine, and to passively stretch the extensor apparatus in order to obtain and maintain a satisfactory postural balance with the lumbosacral angle reduced to a minimum.[3]

Posterior Division Syndrome

All ligamentous, fascial, aponeurotic and muscular tissues derive their sensory supply from the posterior primary division of the spinal nerve, as does the capsular apparatus. Strain or injury of these structures produces pain which is sharp, cutting, and knifelike in character. These lesions also cause a reflex pain which may radiate down an extremity and mimic a nerve root lesion even though the trouble is in the superficial structures and does not involve impingement of a nerve root. This type of referred pain in a lower extremity can emanate from lesions far removed from the intervertebral disc and the nerve roots but is most often confused with a prolapsed lumbar intervertebral disc because of the referral component of the pain. In most of these cases there is a trigger point located in a structure close to the surface. This usually is at a point of ligamentous or muscular attachment, particularly the erector spinae origins.[4]

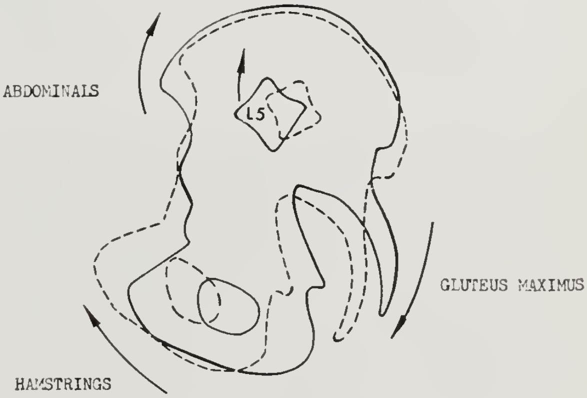


FIG. 2. Diagram showing how forward tilting of pelvis causes decrease in lumbosacral angle.

The procaine test is helpful in differentiating these lesions. If, after the local injection of procaine at the trigger point, the following 5 postulates can be met, a diagnosis of posterior division syndrome can be confirmed: First, contact with the needle inserted for the injection of the procaine must aggravate the local pain experienced by the patient; second, the needle point contacting the lesion should elicit or accentuate the referred pain in the lower extremity; third, the procaine infiltration must decrease the local tenderness; fourth, the procaine infiltration must suppress the referred pain; and fifth, positive leg symptoms or complaints must disappear. When these postulates are met, the test is considered positive and the radiating pain is a reflex phenomenon originating in a superficial lesion and not a true referred pain as seen associated with root impingement.[5]

Symptoms of the Usual Acute Postural Back Problem

A history is often given of repeated episodes of acute low back pain initiated by forceful hyperextension. Between attacks hyperextension movements of the back increase the pain, whereas flexion reduces it. Examples of hyperextension include sleeping on the abdomen, sitting in an erect attitude, bending over a wash basin, lifting a load in front of the body at or above waist level, and rising from a sitting position.

The patient stands with a flexion attitude to relieve the ligamentous strain. Localized tenderness is observed about the lumbosacral junction. In the acute stage the back muscles are in spasm and motions are restricted in all directions. An increased lumbar lordosis and rounding of the dorsal spine may be noted. A neurologic examination is necessary to determine or exclude nerve root irritation.

Treatment

Treatment should be directed at reducing lumbosacral extension, thus shifting the center of gravity forward and relieving the posterior pressure at the lumbosacral junction. To accomplish this it is necessary to actively stretch the extensor apparatus in order to obtain and maintain a satisfactory postural balance with the lumbosacral angle reduced to a minimum.[6] The Williams' flexion exercises[3] are excellent for this purpose.

In the treatment of the acute stage it is often necessary to admit the patient to the hospital for a period of bed rest in a position of flexion. The patient should be placed in the semi-Fowler's position with the application of pelvic traction. Medication should be directed at relieving pain and muscle spasm. The application of moist heat and administration of analgesics and muscle relaxants, such as Phenaphen® no. 2 every 3 hours and Valium® 5 mg., 3 times daily, are directed toward this end. After the acute episode has subsided the patient is started on an exercise regimen in order to improve his body mechanics and is instructed in dynamic posture building.

Exercises

In order to receive future benefits from any exercise program to prevent back pain, the patient must be conscientious and diligent in his efforts. He must be posture-minded, continuously correcting his posture by voluntary effort until it becomes second nature. Only then can he expect to be free of pain.

The Williams' exercise program is directed at actively developing the flexor muscles of the lumbosacral spine and passively stretching the extensor muscles and fasciae (figure 3). The group of exercises should be done twice daily, with the number of times each exercise should be performed varying with the individual case.

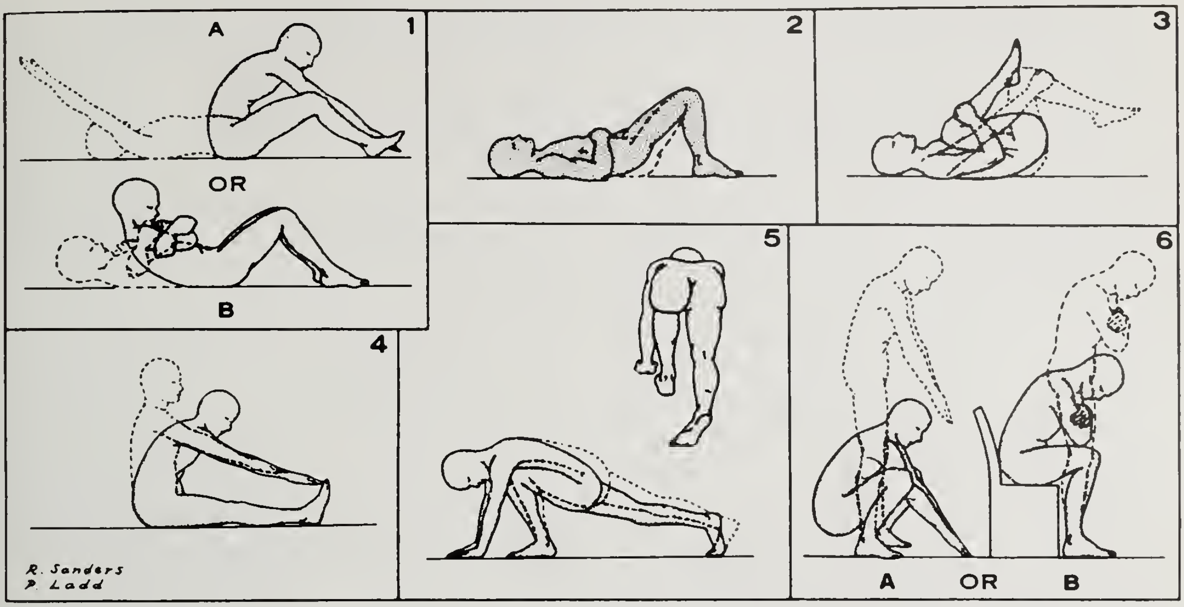
Exercise no. 1 is directed at actively developing the abdominal muscles. The feet may have to be anchored under a support in order for some patients to come to a full sitting position.

Exercise no. 2 is directed at developing the glutei maximi. The pelvis is rotated forward by an active contraction of these muscles. Flexion should take place only at the lumbosacral spine, and the remainder of the back should remain flat on the floor.

Exercise no. 3 is directed at passively stretching the erector spinae and the contracted fasciae and the ligaments posterior to the center of gravity at the lumbosacral level. As this is accomplished flexion is restored to the lumbosacral spine. The knees should be pulled back and forth in an effort to bring them into the axillae. The aim of the exercise is to lift the buttocks off the floor, thus concentrating the action to the lumbosacral level.

Exercise no. 4 also stretches the erector spinae but is more important in stretching short hamstring muscles in those patients who have experienced protective hamstring spasm over a long period of time. It should not be employed in those who are experiencing radiating pain into

POSTURAL INSTRUCTIONS



Exercises should be taken on padded floor____bed____.

Exercise 4 should be omitted unless otherwise instructed.

Start exercises by doing each one________times morning and evening, increasing the series one a day until you are doing each one________times morning and evening.

Exercises are essential in obtaining a proper muscular balance but a correct posture is acquired only through conscious effort.

Remember—

1. When standing or walking, toe straight ahead and take most of your weight on heels.
2. Try to form a crease across the upper abdomen by holding the chest up and forward and elevating the front of the pelvis. Walk like you were going up an incline.
3. Avoid high heels as much as possible.
4. Sit with the buttocks "tucked under" so that the hollow in the low back is eradicated.
5. When possible, elevate the knees higher than the hips while sitting. This is especially important when driving (driver's seat forward) or riding as a passenger in an automobile.
6. Sleep on your back with knees propped up or on your side with one or both knees drawn up. Bed should be moderately firm.
7. Do not lift loads in front of you above the waist line.
8. Never bend backwards.
9. Do not bend forward with knees straight. Always "squat."
10. Avoid standing as much as possible.

Learn to Live 24 Hours a Day with the Hollow in the Lower Part of Your Back Reduced to a Minimum

FIG. 3. The 6 Williams' flexion exercises. Reproduced by permission from Williams, P. C.: The Lumbosacral Spine. Copyright, 1965, McGraw-Hill, Inc. All rights reserved.

the extremity but should be instituted as soon as segmental symptoms have been relieved.

Exercise no. 5 is intended to stretch anterior thigh and hip structures which limit extension of the hip joint. These consist primarily of the fascia lata and the iliofemoral ligament. The foot on the flexed extremity should be placed and remain flat on the floor, while the foot on the extended extremity should be dorsiflexed so that weight is borne on the ball of the foot and externally rotated so that major tension is applied to the anterolateral aspect of the thigh. By flexing the forward knee the pelvis is moved up and down, the downward motion being effective in stretching the structures. The knee should remain in the extended position during the entire exercise if possible.

Exercise no. 6 is the "flat-footed squat" and is very effective in maintaining a muscle balance as well as preventing extension contractures of the lumbosacral spine. It has the additional value of strengthening the leg muscles, especially the quadriceps group, weakness of which is usually responsible for a person bending from the hips with the knees extended rather than squatting up and down during the course of his daily routine. The heels should remain flat while the hands touch the floor with the elbows between the knees.

Discussion

The remedial muscle training program and postural instruction, when performed early enough and adequately enough, minimize the mechanical stress affecting the lumbar spine, particularly the lumbosacral area. If the basic faults are not sufficiently treated the problem may well progress to the point of rupture of a lumbar disc with its increased morbidity and disability. Hence this program of early recognition and adequate treatment of faulty lumbosacral mechanics can be said to be the best of preventive orthopedics as applied to the low back problem.

While there are many causes for low back pain, the great majority of patients seen by the generalist have a postural basis as the etiology. An understanding of the pathomechanics involved will aid in the application of effective treatment in the acute case and encourage the use of posture building and remedial muscle training exercises as a preventive measure in the patient with a chronic low back problem.

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Rhegmatogenous Retinal Detachment*

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As THE PRIMARY OPTIC VESICLE invaginates to form the optic cup the distal portion of the vesicle gradually approaches the proximal portion until the 2 neuroectodermal layers are separated by a potential space only. Except at the extreme anterior periphery of the mature retina and at the optic disc these layers, which develop into the rod and cone layer and the pigmented epithelial layer, are not firmly attached. Rhegmatogenous retinal detachment is a separation of these layers with accumulation of subretinal fluid in that potential space (figure 1).

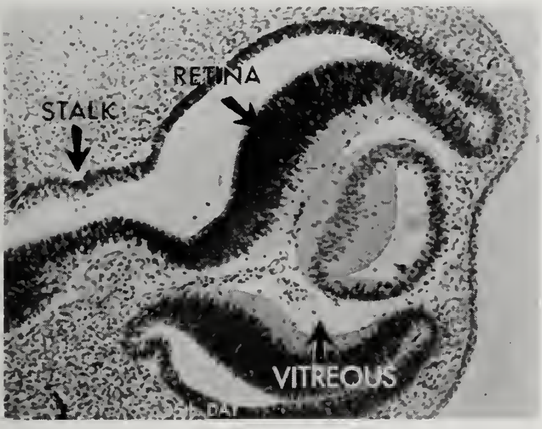

FIG. 1. Demonstration of the potential space formed by the invaginating neuro-ectodermal layer of the optic vesicle. This forms the line of cleavage in retinal detachment.

The mechanism for the accumulation of this fluid is the escape of fluid from the vitreous into the subretinal space through a hole or tear (break) in the retina (figure 2). Although the exact cause is unknown, factors which favor the formation of these tears or holes are degeneration of the peripheral retina on the basis of age or arteriolosclerosis with adhesions forming between the retina and the vitreous body.

Rhegmatogenous (Greek *rhegma* meaning break) retinal detachment is to be carefully distinguished from those detachments which may be associated with various vascular retinopathies, including retinopathy of prematurity, choroidal, retinal and metastatic tumors, uveal and vitreous inflammation, uveal effusion, splitting of the retina, and choroidal detachment.

It has been estimated that 4 to 5 per cent of the population have asymptomatic retinal tears, but fortunately only a small percentage of these progress to become symptomatic or lead to retinal detachment. A majority of these cases are concentrated in patients between 40 to 70 years old, with a predilection for males, and patients with myopia. The condition is bilateral in 25 to 30 per cent of cases.

Signs and Symptoms of Retinal Detachment

One of the first symptoms of detachment may be the sudden appearance of flashes of light which indicate localized vitreous traction on the retina; these may precede or accompany the formation of a retinal break, and they may be accompanied by showers of black spots and vitreous "floaters," i.e., vitreous opacities from hemorrhage caused by a tear in a retinal vessel by the retinal break. Thus, in most cases of vitreous hemorrhage it is necessary to consider detachment as a possible cause. Evidence of diabetic or hypertensive retinopathy does not rule out a detachment; it may occur in association with these conditions.

The appearance of a gray cloud or veil in the patient's field of vision is dependent on the extent and position of the detachment, with loss of central vision occurring when the macula becomes detached. Such loss may be demonstrated quantitatively by perimetry.

Examination of the vitreous with a slitlamp may show a moderate to severe anterior uveitis, pigment scattered throughout the vitreous, or distinct changes in the anatomy of the vitreous body. These changes include collapse of the

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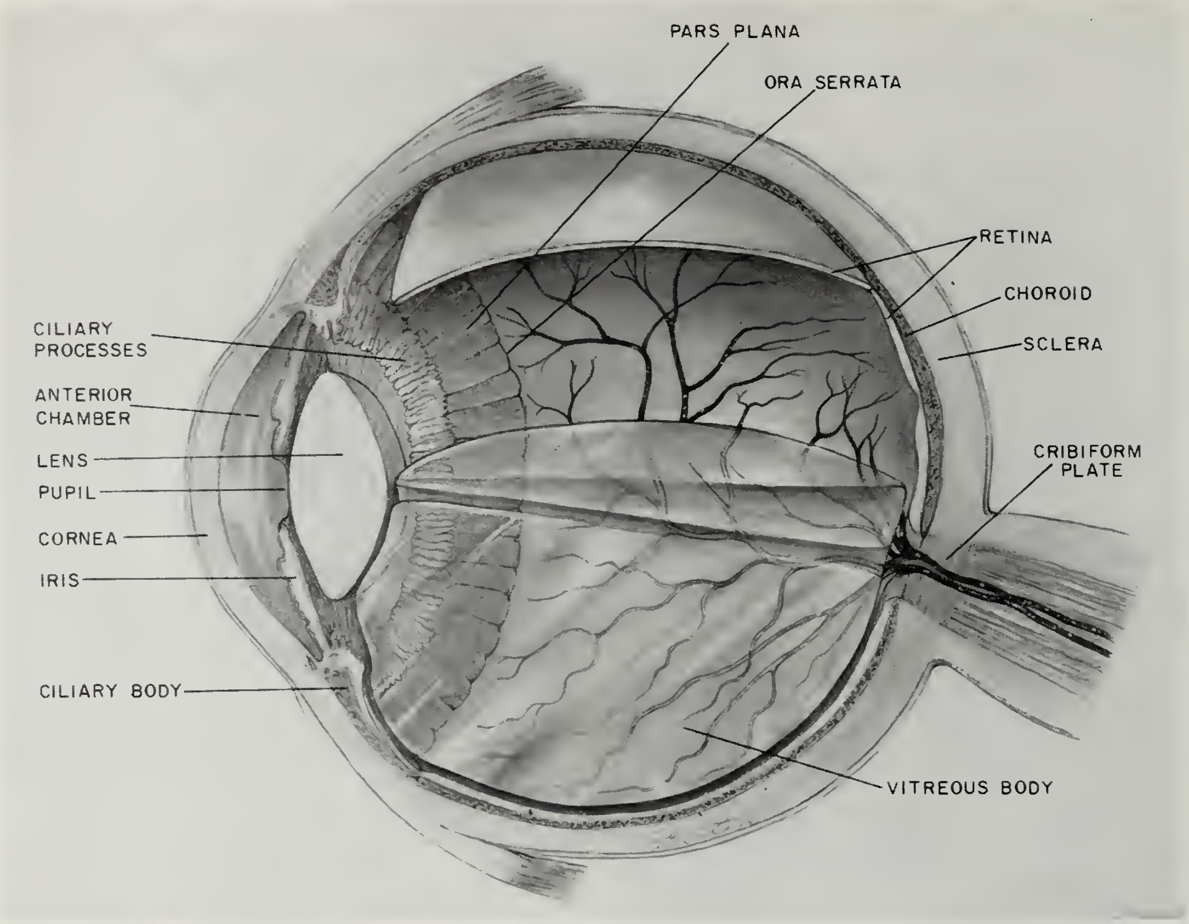

FIG. 2. General anatomy of eye with particular reference to relationship of retina with vitreous body and ciliary body.

vitreous body with detachment of the vitreous from the posterior portions of the eye, and frequently abnormal vitreoretinal adhesions may be observed (figure 3). Localized vitreous liquefaction (syneresis) may also be seen but is of little prognostic significance in cases of detachment. Usually the intraocular pressure is diminished when a detachment occurs, but elevated intraocular pressure may suggest a choroidal tumor, and the association of retinal detachment with glaucoma is not rare.[1]

Examination of the Retina

The binocular indirect ophthalmoscope is the instrument which is most popularly used for the examination of retinal detachment because it affords a large field of vision, stereopsis, and a more comfortable working distance than the direct hand ophthalmoscope. In combination with depression of the sclera the extreme periphery of the retina may be examined stereoscopically and the retinal breaks accurately localized.

A detached retina appears like a translucent veil which generally forms soft, numerous folds that move freely with movements of the globe. The vessels appear more tortuous and have a darker than normal color. The extent of the detachment is not in itself of much prognostic significance, but it often gives a geographic indication as to where the retinal breaks are located. A total detachment may become reattached as well as a partial one, provided that all retinal breaks are located and repaired.

The detachment may extend beyond the peripheral insertion of the retina to the choroid at the ora serrata into the pars plana ciliaris; this situation is observed in cases of trauma, giant retinal breaks, and when there is traction on the attachment of the vitreous body to the retina in the peripheral region (ora serrata).

If detachment has been present for about 3 months a whitish gray or pigmented line, called a demarcation line, may be present at the boundaries of the detached and normal retina.

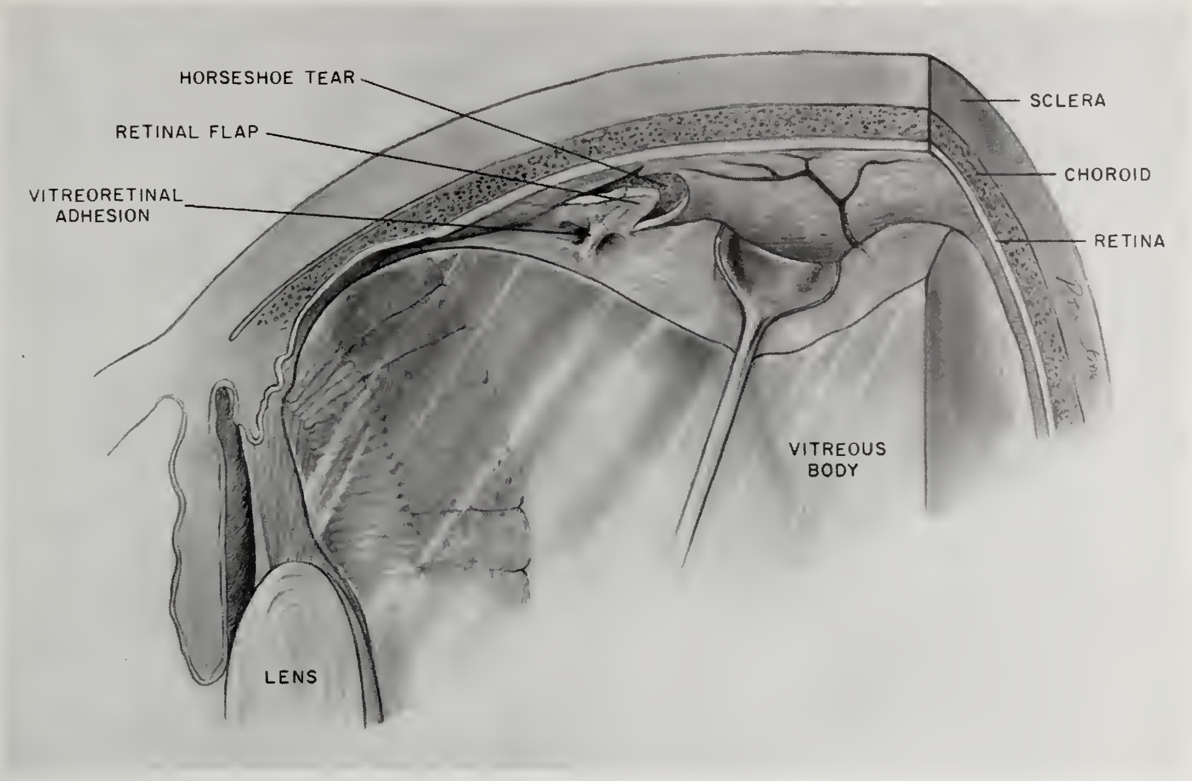

FIG. 3. Relationship of flap of a horseshoe retinal tear with a vitreoretinal adhesion. The hyaloid membrane of the vitreous is depressed for demonstration.

Significance of Retinal Breaks

The importance of the retinal breaks was not understood until about 1929 when Jules Gonin, a Swiss ophthalmologist, showed that detachment was nearly always associated with tears, and that by obturating these tears the retina could be reattached. Prior to his work detachment was essentially untreatable.

These breaks appear as sharply outlined red spots; the red choroidal hue is distinctly contrasted against the surrounding elevated grayish retina. It is sometimes difficult to distinguish a break from a small retinal hemorrhage, and such distinction becomes more difficult if the media are hazy due to opacities in the vitreous, lens, or cornea. Similarly, when a detachment is very flat there is less color contrast between the detached and undetached retina, and thus the breaks are more difficult to distinguish.

The majority of breaks are found between the retinal equator and the more anterior ora serrata (figure 4). (The equator is, roughly, the most peripheral zone of the fundus which can be seen with a hand ophthalmoscope through a well-dilated pupil.) These breaks, often located in the upper temporal quadrant, may be horseshoe-shaped or oval tears. The latter include round or irregular holes which are nearly always multiple, and are found in atrophic and degenerated areas. A particular type of degeneration which predisposes to the formation of such holes is lattice degeneration. This is characterized by white lines arranged as a network, formed by retinal vessels which are either sheathed or completely obliterated. These lesions tend to be bilateral, symmetrical, familial, and perhaps hereditary. Such degenerations are also frequently found associated with partial detachments of the vitreous surface from the retina and with vitreoretinal adhesions.[2]

Breaks may be located exclusively in the area of the ora serrata. The ora serrata shows a scalloped, pigmented line (figure 5). It is the site of attachment of the peripheral retina to the choroid. Each scallop is called an oral bay, and the pigmented projections which extend anteriorly and separate the bays from one another are called oral teeth. These breaks tend to be small and multiple, and may have round, oval, or horseshoe-shaped outlines along the borders or posterior extremities of small meridional retinal folds which form in relationship to the oral teeth. They may be associated with marked chorioretinal degeneration, active peripheral uveitis, posterior cortical cataract, and

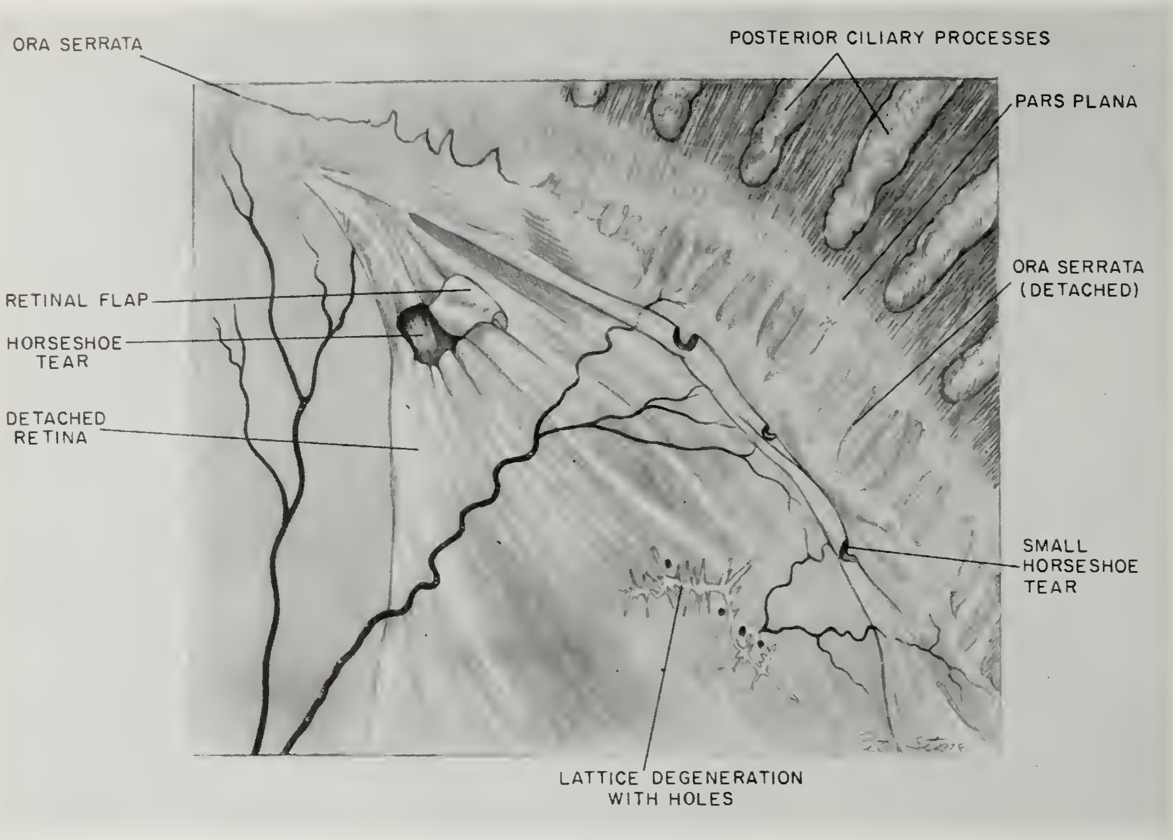

FIG. 4. Extreme anterior retinal periphery demonstrating relationship of ora serrata with ciliary body anteriorly and retina posteriorly. A partial detachment is shown, containing several horseshoe retinal tears and an area of lattice degeneration containing multiple small holes. Detachment extends beyond retina proper onto nonpigmented epithelium of pars plana ciliaris.

open-angle glaucoma. This type of lesion is often seen in those patients who, having had cataract surgery, develop retinal detachment, an incidence of approximately 3 per cent.

Retinal dialysis or disinsertion is another type of break which may occur at the region of the ora serrata. It is more common in young people, is frequently associated with trauma, affects the lower quadrants, and has some tendency to bilaterality. In a number of cases the insertion of the vitreous base to the peripheral retina is torn as a result of the injury; avulsion of the vitreous base is probably the direct cause of a number of traumatic retinal dialyses. A giant retinal break, one which occupies more than 90° of arc, presents special problems in surgical technique.

Significance of Vitreous Pathology

Apart from the detection of retinal breaks, which is of paramount importance, evaluation of the vitreous is essential in regard to prognosis. The extent of vitreoretinal adhesion and organization within the vitreous body is significant.

Ordinarily, folds of detached retinal areas move freely as the eye is moved, and in such cases the detachment often settles following bed rest as the subretinal fluid is absorbed. Elevated retinal folds which do not move freely are called fixed folds which cannot flatten with bed rest because of retinal scarring, vitreous adhesion, or attachment of a preretinal membrane to the edge of the tear or retinal fold.

Fixed retinal folds make the prognosis poor, since they prevent the retina from settling properly. If they are large or located adjacent to each other, special surgical techniques with or without vitreous surgery are required to obtain reattachment of the retina. Occasionally a massive preretinal membrane may develop over the posterior retina and over the posterior surface of the detached hyaloid membrane of the vitreous; this may cause the entire retina to become detached and fixed. The prognosis here is not favorable.

Surgical Management

Once retinal breaks have been localized and the fundus thoroughly investigated by indirect ophthalmoscopy, the management is determined by the type of detachment found and by the location and characteristics of the breaks. The basic principle in detachment surgery is to seal accurately the break by means of a scar formed around the break between the retina and the choroid, with evacuation of subretinal fluid.

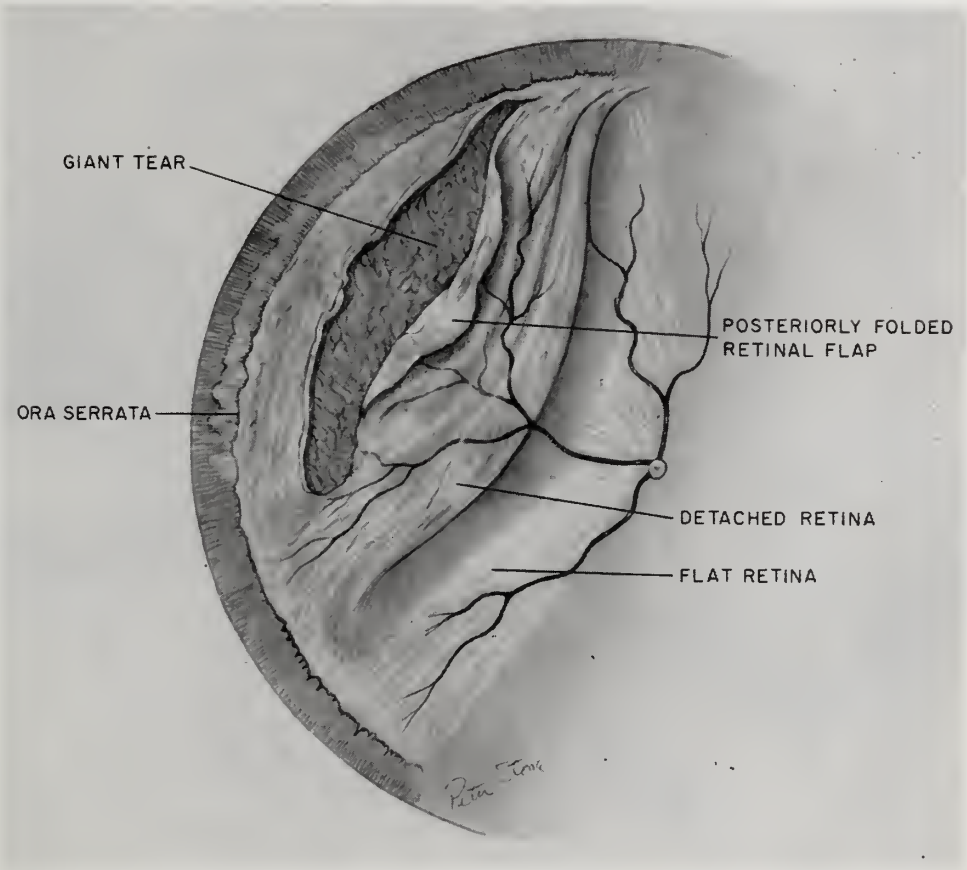

FIG. 5. A giant retinal tear demonstrating rolled posterior flap and bullous retinal detachment.

These scars are commonly produced by diathermy, whether directly applied to the sclera overlying the tear or by producing an inflammatory reaction in this region by means of heat generated in these tissues through the pupil by light coagulation or the ruby laser. Courrently cryosurgical techniques are being utilized to produce the desired inflammatory reaction with certain advantages over standard diathermy techniques in selected cases. Often it is necessary to indent the sclera in the area of the tear to more closely approximate the diathermy area to the elevated tear by the various techniques of scleral buckling. Such buckles are usually produced by implantation of a silicone plate in a bed prepared in the sclera directly over the tear into which diathermy has been previously placed. The result is to indent the area of diathermy in toward the retina when the scleral flaps are closed over the silicone plate. This buckle can be made permanent by encircling the eye with a silicone band, held in position by anchoring sutures, and overriding the silicone plate. The indentation produced by the plate will be temporary only if an encircling band is used.

If the surgeon prefers nonbuckling procedures, it is important to try to induce absorption of the subretinal fluid by immobilizing the eyes at strict bed rest. The patient is considered to be ready for surgery when no further flattening of the retina may be expected. In cases with either fixed retinal folds, preretinal retraction, or retinal breaks with rolled convex edges improvement with bed rest is slight to absent. Such failure to improve may also be caused by the

(*Continued on page 518*)

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Contraindication: Not recommended during pregnancy.

Caution: May be habit-forming. Do not use in patients sensitive to barbiturates or in those with moderate to severe hepatic disease.

Side Effects: Nausea, transitory dizziness, rash. Overdosage of allobarbital produces symptoms typical of acute barbiturate excess.

Dosage: *Adults:* 1 or 2 tablets every 4 hours. Not to exceed 8 tablets in 24 hours. *Children 6 to 12:* ½ to 1 tablet every 4 hours. Not to exceed 4 tablets in 24 hours.

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3-6 months	3 mg.	½ tsp. 3 times daily
6-12 months	4 mg.	½ tsp. 4 times daily
1-2 years	5 mg.	½ tsp. 5 times daily
2-5 years	6 mg.	1 tsp. 3 times daily
5-8 years	8 mg.	1 tsp. 4 times daily
8-12 years	10 mg.	1 tsp. 5 times daily

Adults: 20 mg. (2 tsp. 5 times daily or 2 tablets 4 times daily) Based on 4 cc. per teaspoonful. Maintenance dosage may be as low as one-fourth the initial daily dose.

Precautions: Lomotil, brand of diphenoxylate hydrochloride with atropine sulfate, is a Federally exempt narcotic preparation of very low addictive potential. Recommended dosages should not be exceeded. Lomotil should be kept out of reach of children since accidental overdosage may cause severe respiratory depression. Lomotil should be used with caution in patients with impaired liver function and in patients taking addicting drugs or barbiturates. The subtherapeutic amount of atropine is added to discourage deliberate overdosage.

Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness, insomnia, numbness of extremities, headache, blurring of vision, swelling of the gums, euphoria, depression and general malaise.

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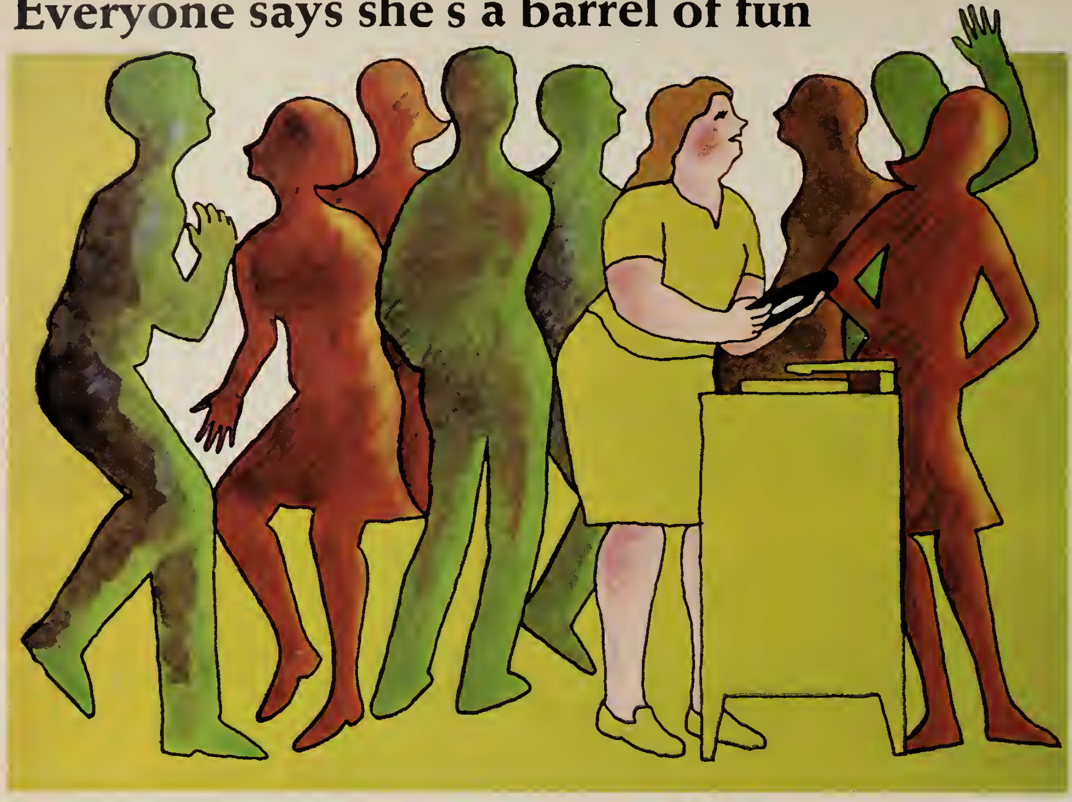
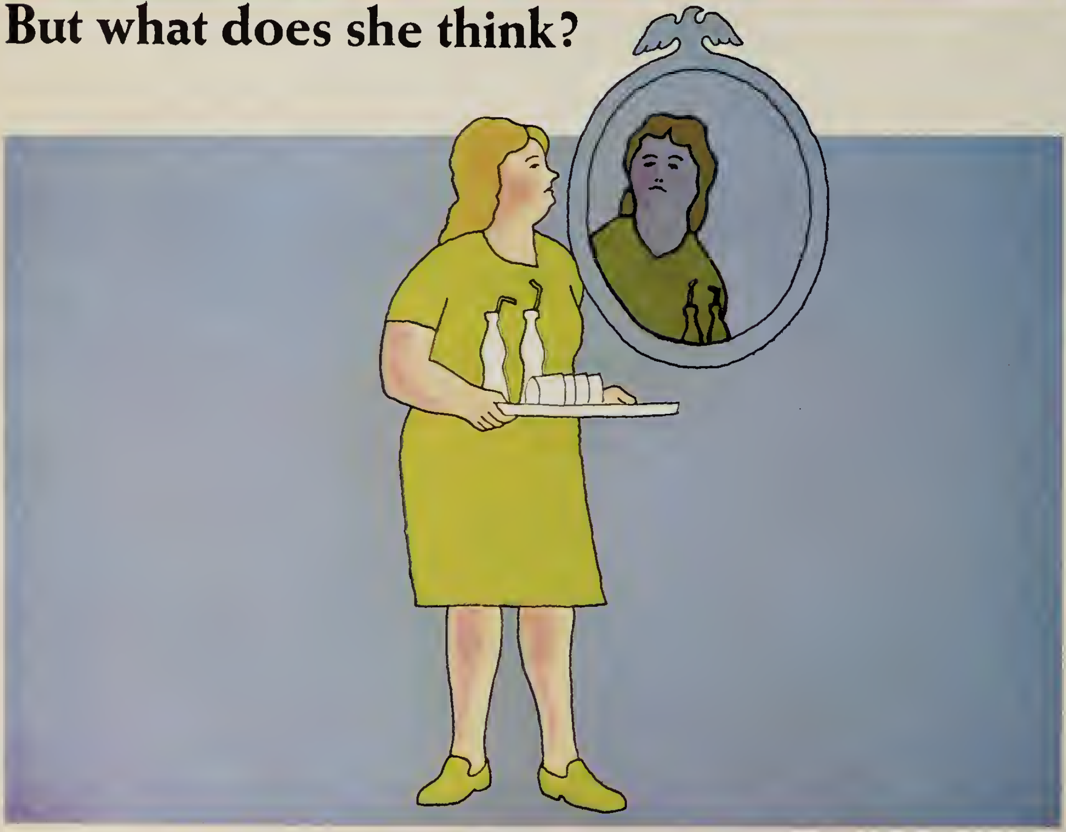


But what does she think?



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Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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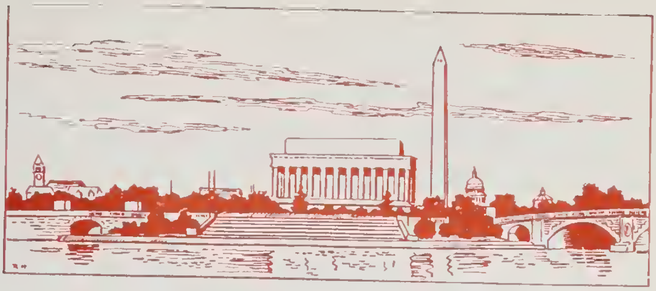
PRESIDENT'S PAGE

THE FORTHCOMING SOUTHERN MEDICAL ASSOCIATION MEETING

At the time of the 1956 meeting of the Southern Medical Association in Washington, the Medical Society of the District of Columbia cancelled the Annual Scientific Assembly that was scheduled for approximately the same time. Our Society actively participated in the planning and conduct of the Southern Medical Association meeting, one entire half-day program being presented by the Medical Society of the District of Columbia.

This previous meeting proved so successful and rewarding to our membership that a decision was made to again merge the Annual Scientific Assembly with the Southern Medical Association meeting to be held at the Washington Hilton Hotel on November 14–17. Since the program of this meeting is being developed along sectional lines, our Society will not provide a separate program, but instead members of our Society will be called upon to participate in the individual programs of the 22 Sections that will be held throughout the 3-day period. It is hoped that not only will those of our members who are approached concerning participation respond favorably but also that members who wish to present a paper will approach the local member of the Southern Medical Association who is in charge of the appropriate sectional program.

All members of the Medical Society of the District of Columbia are eligible to attend the meeting without charge, and it is hoped that attendance from our Society will be no less than that which takes place at our Annual Scientific Assembly.



EDITORIALS

Community Health Week—October 16–22, 1966

"Abstain"—"Invest in Your Health"—"Avenues to Good Health"—"An Ounce of Prevention"—"Good Health, Your Personal Challenge"—all of these have been suggested as slogans for Community Health Week 1966. Your Medical Society is committed to making this Nationwide, AMA-sponsored observance bigger than ever. It is hoped that through our efforts a greater public awareness and appreciation of the wealth of health facilities and services available in our community will be achieved.

The health team supporting Community Health Week 1966 includes: the D. C. Diabetes Association, the D. C. Dental Society, the Prevention of Blindness Society of Metropolitan Washington, the Graduate Nurses' Association of D. C., the Washington Heart Association, the D. C. Cancer Society, the D. C. Department of Public Health, the Dairy Council of Greater Washington, D. C. Dietetic Association, local hospitals, and all Sections of the Medical Society of the District of Columbia.

Present plans call for: health exhibits at the Medical Society building, screening tests for glaucoma and diabetes, chest X-ray screening, drug store displays, window displays in multiple store areas throughout the city, posters on the D. C. Transit buses, speakers and panels for radio and television, a health quiz for newspaper publication, a Community Health Week Luncheon with presentation of the John Benjamin Nichols Lay Award, the Robins Community Service Award, and the Medical Society's Certificate for Meritorious Service to one or more meritorious members of the profession.

All members of the Medical Society are invited to participate and are urged to support our efforts in sponsoring Community Health Week 1966. PARTICIPATE! Be a speaker when asked. Encourage your patients and friends to visit the Medical Society exhibits. Attend the Community Health Week Luncheon. Let's make our Washington residents more keenly aware of the many community services which medical advances and progressive health organizations are making available to them.

Warren D. Brill, M.D.
Chairman, Committee on Public Information and Education

Psychiatry in Washington

Elsewhere in this issue (page 501) Mr. Paul Hencke, a gifted writer and commentator on the Nation's affairs, turns his searchlight on the practice of psychiatry in Washington. Originally given as a lecture to the members of Zonta, entitled "Psychology and Psychiatry in Washington," the piece gives a broad overview of the kind of problems which find their way to the psychiatrist's consulting room and to the analyst's couch. As such it is well worth reading.

The psychiatrist with a medical orientation, however, will note certain omissions. To the medical observer, Washington psychiatry is a psychiatry of contrasts. Mental hospital psychiatry is at one end of the spectrum, adequately represented by St. Elizabeths and D. C. General Hospi-

Opinions expressed in contributions to the Editorial Section are those of the writers and do not necessarily reflect the views of the Medical Society of the District of Columbia

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tals. Psychoanalysts and analytically-oriented psychiatrists are at the other end of the spectrum. There are only 4 general hospitals (George Washington, Washington Hospital Center, Freedmen's, and Sibley) which have psychiatric units. No private psychiatric hospitals exist within the District limits. In spite of the fact that there are over 500 psychiatrists listed in the most recent directory published by the Washington Psychiatric Society, there are only a precious few "general" psychiatrists who regularly, and by choice, combine hospital and office practice. It is this category of psychiatrist which is in short supply and in greatest demand in Washington.

The historical reasons for this dilemma are fairly obvious. For many years St. Elizabeths Hospital dominated the psychiatric scene in Washington. Since World War II the analytic institutes, the medical schools, and the Washington School of Psychiatry have played an increasingly important role in influencing young psychiatrists in the direction of one-to-one office psychotherapy. What is now desperately needed is a "new look" in the training programs of the Departments of Psychiatry in all the local medical schools with much greater emphasis placed on the training of general psychiatrists. If we had enough young men with such training to take leadership we could easily have a psychiatric unit in every voluntary hospital in the Washington Metropolitan Area. This would bring psychiatry and medicine closer to each other and thus greatly improve the picture of "Psychiatry in Washington."

Z. M. L

Hospital Facilities Available for More Specialists in Southeast Washington

SOUTHEAST WASHINGTON and nearby Prince Georges County's egg-hen situation will probably be resolved soon. The 400,000 residents of this still-growing area have always lacked a sufficient number of physicians, particularly specialists and subspecialists. For years the academic question prevailed: Which comes first, a first-class hospital to attract physicians or enough physicians to encourage a first-class hospital?

An answer with profound impact came on April 12 of this year when the Morris Cafritz Memorial Hospital opened its doors to patients. The Hospital is a 380-bed, 9-level facility offering complete general surgery, medicine, emergency, pathology, pharmacy and radiology services at the present time. Before the year is over obstetrics and gynecology, pediatrics, psychiatry, physical medicine and rehabilitation, outpatient and long-term care services will be phased in.

The presence of a properly equipped, efficiently designed community hospital won't result in an immediate exodus of doctors to Southeast Washington. However, in the few short months the Hospital has been open it has become apparent that the movement to Southeast is not far away.

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Urologists, dermatologists and ophthalmologists will find the Cafritz Memorial facilities inviting. Medical neurologists, especially, will be attracted by the most modern radioisotope laboratory.

Cafritz Memorial is a tribute to a community that needed the facilities that only a hospital can provide, labored for 13 years to build one, and when it was completed had not only a modern plant but a model community hospital for all the Nation to copy.

FRANK S. PELLEGRINI, M.D.
President of the Medical Staff,
Morris Cafritz Memorial Hospital

Report of the Delegates to the AMA House of Delegates

Chicago, June 26–30, 1966

THE RECENT MEETING of the House of Delegates in Chicago was the most intense and hectic of those which it has been the privilege of your delegates to attend. Sessions were prolonged, discussion involved and at times heated, and the rules of parliamentary procedure were invoked more than ever in the past.

With all, the meeting was very constructive, and policies were established and reaffirmed which should be of immense value to the profession in the future.

A large number of reports and resolutions dealing with the Medicare law and other Federal laws or programs were received and considered. The report from the Board of Trustees on Medicare was particularly informative in its discussion of direct billing, the basic principles of utilization review, the principle of rejection of compensation for service on utilization review committees, and the necessity for the proper placement of responsibility for any failure in the Medicare program. The House, in approving the report, commended the Board for its diligent and productive efforts in assisting in the implementation of the law. Its efforts resulted in simplification of some forms, the elimination of others, the publication of a "Reference Guide" for physicians, and numerous changes in regulations and procedures.

The Board will continue to supply advice, guidance and dissent, when necessary, to the Government or other third parties on matters that pertain to the health of the public and the interests of the medical profession.

The information in the report will receive wide dissemination to the profession.

The House strongly supported the concept of individual responsibility. Report E (A-66) of the Council on Medical Service recommended reaffirmation of the responsibility of physicians for determining how they will govern their professional practices under the Medicare law, and that physicians should be made acutely aware of the manifest superiorities of direct billing. Report E will be given the widest possible distribution and will be published in its entirety in an early issue of *The AMA News*.

Three resolutions which recommended that physicians use the direct billing method under PL 89-97 rather than the assignment procedure were adopted. The House in doing this pointed out that these resolutions should not be interpreted as contravening the statement approved at the special session in October 1965 which read:

"The American Medical Association opposes any program of dictation, interference or coercion, whether direct or indirect, affecting the freedom of choice of the physician to determine for himself the extent and manner of participation or financial arrangement under which he shall provide medical care to patients under Public Law 89-97."

In considering a resolution on the right to bill patients under Title 19 of the law, the House passed an amendment pointing out that direct billing has been recommended as the billing method of choice under Title 18 by the Board of Trustees and the Council on Medical Service. It then said that since there is a wide latitude available to the states in establishing administrative procedures under Title 19, each state medical association should work early and diligently in its own state so that any plan or law adopted in its state for approval under Title 19 would include authorization for direct billing.

The House also instructed the AMA Advisory Committee to the Department of Health, Education, and Welfare to do all in its power to implement the intent of the resolution at the national level. In addition, the House urged positive steps to obtain statutory authority for a continuing medical advisory committee under Title 19, and it called on the AMA and the state societies to maintain added vigilance to eliminate any patterns which might subvert the intent of Title 19.

Two resolutions involving billing and reimbursement of hospital-based physicians are mentioned here because of their significance to all physicians and in particular hospital-based specialists. The first said:

> "The Principles of Medical Ethics declare that a physician shall not dispose of his services to a third party or 'lay' organization; and
>
> "Title XVIII of Public Law 89-97 recognizes the principle of the separation of professional and hospital costs for services rendered by hospital-based physicians; and
>
> "This principle has been advocated by the AMA, the American College of Radiology, the American College of Pathologists, and many regional organizations; and
>
> "A great number of hospital-based physicians throughout the Nation have declared their intention to bill separately for their professional services in keeping with this principle; *therefore be it*
>
> "*Resolved*, That, since separate billing by the physician for his professional services is a preferred ethical practice, it shall be deemed unethical for a physician to displace a hospital-based physician who is attempting to practice separate billing when said displacement is primarily designed to circumvent separate billing."

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The second resolution regretted that publication of Medicare Regulation No. 5 was delayed until June 28, 3 days before the effective date of Medicare, and said that these regulations do not conform to the intent of Congress as expressed in Section 1801 of the Medicare law. It then declared that:

> "The House of Delegates instruct the Board of Trustees and the Executive Vice President to request from the Social Security Administration an extension of date of final adoption of the proposed regulations of not less than 90 days, in order that the American Medical Association and all other interested medical organizations be allowed reasonable time to study and to submit to the Social Security Administration data, views or arguments, and pertinent constructive comments and suggestions.
>
> "To preserve the professional independence of medical practice, that the Board of Trustees and officers of the AMA be instructed to immediately inform the membership that Medicare Regulation No. 5 will not apply to physicians (whether hospital-based or not) who (1) have no financial relationship with a hospital covering medical services to patients; (2) do not accept assignments but bill directly.
>
> "*The AMA News* and other appropriate media be used to advise all physicians who are developing contractual relationships with hospitals for professional service that they should delay the finalization of any agreements pending further analysis of the implementing regulations."

The question of the propriety under medical ethics of a physician owning a pharmacy or dispensing of drugs or appliances, including eye glasses, was thoroughly thrashed out again. A Board of Trustee's proposal that such practices were permissible only when approved locally was not adopted. In its place, a reference committee statement reaffirming the principle that "drugs, remedies or appliances may be dispensed or supplied by the physician when it is in the best interests of the patient" was adopted. The crux of the matter lies in the interpretation of the words "in the best interest of the patient." In 1963 the House of Delegates gave its interpretation to the phrase. In essence it was that the physician must exercise sound judgment in dispensing and must not do so solely for his convenience or for the purpose of supplementing his income.

Of interest to every member will be the dues increase of $25. Effective January 1, 1967 AMA dues will be $70 per year. This increase was voted by a 4–1 majority after prolonged and thoughtful discussion of all the pros and cons and the consideration of several alternatives offered as substitutes. It was the feeling of the House that the programs necessary to serve the needs of the members of the AMA cannot be conducted effectively without adequate financing, and such financing would be impossible without the dues increase as voted.

In asserting its awareness of the present and future shortages of medical manpower the House adopted the following reference committee statement:

"Your Reference Committee is well aware of the drastic shortage of health manpower that is confronting the American public. It is keenly appreciative of the opportunity presented to the American Medical Association to furnish leadership in the solution of this problem. The necessary additional manpower in the medical profession and in allied health professions must be developed. The most effective and efficient utilization of existing health manpower must be made at all times. This is no time to surrender leadership to persons or organizations outside of the medical profession."

In all, 106 resolutions, 38 Board reports, and 20 additional reports from councils and other groups were considered. A few of the more significant ones will be mentioned.

The Council on Constitution and By-laws was authorized to prepare such changes in the Constitution and By-laws as would be necessary to permit the Judicial Council to receive and act upon appeals filed by applicants who allege they have been unfairly denied membership in a local and/or state society.

Constituent medical associations are urged to oppose as detrimental to the public interest any proposed legislation that would authorize optometrists to engage in the diagnosis or treatment of diseases of the eye. This came about through the introduction of a resolution from Tennessee opposing the proposed new optometry law for the District of Columbia. Your delegates supported this resolution in the reference committee and in the House.

The House condemned the abuse of LSD and other non-narcotic drugs and again opposed the compulsory regulation of any single method, such as the use of generic terms, for the prescribing of drugs.

Your delegates introduced 3 resolutions. One, relative to the requirements for calling special meetings of the House, was modified to the effect that the 25 members of the House signing the request be acting in the name of no less than ⅓ of the state associations. The modification was quite satisfactory. Another had reference to council and committee appointments. This too was modified after discussion with your delegates, and a substitute requiring that no physician shall be appointed to a council or committee of the AMA

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unless he is an Active member of the Association, and that notice of his appointment will be sent to his state and county society was adopted. The third resolution was introduced following action taken by this Society at its last Annual Meeting and had to do with the number of hospital meetings, particularly departmental meetings, which a physician with several staff appointments is required to attend. This resolution was not adopted, on recommendation of the reference committee, which, while stating its complete sympathy with the intent of the resolution, pointed out that joint meetings of several staffs under Medical Society auspices would not fulfill the basic reasons for such monthly meetings, which are to review, analyze, and evaluate the clinical work of its members and for the consideration of selected cases, including deaths, infections, complications, errors in diagnosis, the results of treatment, etc. It was further pointed out that the Joint Commission on Accreditation of Hospitals' standards currently provide a choice of methods to accomplish this, and the method chosen need only be "determined by the medical staff and clearly stated in the bylaws." Medical societies and medical specialty societies are urged to take cognizance of the existing flexibility of J. C. A. H. requirements relative to medical staff meetings and to incorporate appropriate provisions in their By-laws and Rules and Regulations.

In an additional action the House adopted a resolution urging that hospital governing boards include physicians in their membership but that the method of this inclusion be a matter of local determination. State and local medical societies are urged to seek the coöperation of their respective hospital associations to implement this action which is now the stated policy of the Association.

Report C (A-66) of the Council on Medical Service included a Model Emergency Department Agreement which should be of interest to and carefully considered by all physicians and hospitals that now or in the future are interested in establishing Emergency Room medical service as an ancillary service of a hospital.

Retiring President James Z. Appel told the House that physicians "must participate in the ranks of both political parties and have a voice in the determination of party policy and the writing of party platform."

President Charles L. Hudson declared that "we shall need all of our intellectual and scientific resources to cope with the new economics of medicine" and to prevent the extension of the Medicare program without demonstrated need toward a

Resolution 103—Psychophysiological Effects of Heat

Introduced by: Gordon B. Smith, M.D., Delegate from Vermont
Subject: Psychophysiological Effects of Heat
Referred to: Reference Committee on Miscellaneous Business (C. Willard Camalier, Jr., M.D., Chairman)

Wheras, The Annual Convention of the AMA is customarily held in the month of June; and

Whereas, The month of June, in the Northern Hemisphere, has long been one of the hottest months of the year; and

Whereas, Delegates to the AMA who are assigned non-air-conditioned rooms, become, as a result of sleepless nights and frenzied frustration, dull, irritable and inefficient delegates; *therefore be it*

Resolved, That in the future full air-conditioning be considered as a prerequisite in the selection of the headquarters hotel for the annual AMA Convention.

In considering Resolution 103, your Reference Committee recognized that this document, without doubt, was conceived in desperation engendered by heat, but was probably presented in icy silence. We want to assure our non-air-conditioned colleagues that your Reference Committee spent long hours in perspiration-soaked shirt sleeves considering Resolution 103.

Your Reference Committee is of the opinion that air-conditioning provides no guarantee of alert, responsive, and effective delegatemanship. Nor are we in complete agreement from previous observation that it prevents sleepless nights or frenzied frustration.

We have been assured, on the positive side, that the psychophysiological effects of heat are readily reversible and convalescence is short. Accordingly, despite our sympathy for our non-air-conditioned colleagues we were able to consider this important matter in the cold light of reason and without heated emotions and rancor.

We are heartened, however, by the assurance that for the foreseeable future only air-conditioned facilities have been engaged for the Annual Conventions. This excepts certain fortunate sites that through a lucky providence have their own outside, built-in air-conditioning.

Your Reference Committee recommends that the *Resolved* of Resolution 103 be modified by the addition of the following words: "in those cities where the psychophysiological effects of heat may interfere with effective delegatemanship," so that this *Resolve* would read:

"*Resolved*, That in future full air-conditioning be considered as a prerequisite in the selection of the headquarters hotel for the annual AMA Convention in those cities where the psychophysiological effects of heat may interfere with effective delegatemanship."

Mr. Speaker, I move the adoption of this section of the report.

C. WILLARD CAMALIER, JR.
Chairman

national health service. He later warned that the real threat to our system of medicine is not in the details of Medicare implementation but in the expansion of the principle of social insurance.

Milford O. Rouse, of Dallas, Texas, was elected President-elect. Dr. Rouse has served for the past 4 years as Speaker of the House of Delegates and before that as Vice Speaker.

Eli S. Jones, of Hammond, Indiana, was elected Vice President; Walter C. Bornemeier, of Chicago, Speaker of the House; and Russell B. Roth, of Erie, Pa., Vice Speaker.

Reëlected to the Board of Trustees were Dwight L. Wilbur and Homer L. Pearson. Elected for their first terms were Burtis E. Montgomery and Max H. Parrott.

The election of Dr. Roth as Vice Speaker left a vacancy on the Council on Medical Service. The Board of Trustees offered the name of James J. Feffer in nomination for this position along with that of John R. Kernodle, of Burlington, N. C., a member of the House of Delegates. There were several nominations from the floor. Your delegates seconded the nomination of Jim and gave him such support as they could, but Dr. Kernodle was elected on the second ballot.

Your junior delegate, C. Willard Camalier, served as chairman of the Reference Committee on Miscellaneous Business. His report, which included a humorous item[*] having to do with the psychophysiological effects of heat and their bearing on effective delegatemanship, was well received, and he was justly praised for it.

In all, it was quite a meeting, and your delegates were ready for the trip back to Washington.

Respectfully submitted,
Raymond T. Holden, M.D.
C. Willard Camalier, Jr., M.D.
Delegates
Clifton R. Gruver, M.D.
Thomas M. Peery, M.D.
Alternate Delegates

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[*] Editor's note: See Resolution 103, above. From our Washington readers, especially, this plea from the Vermont delegate will evoke warm confirmation.

Psychology and Psychiatry in Washington*

PAUL HENCKE

Associate Editor, The Kiplinger Letters; formerly Associate Editor, Nation's Business

OF OUR CITY'S MANY CLAIMS to distinction, one might seem a dubious honor indeed. It turns out that Washington has more psychiatrists per capita than any other major community in America—more than in New York and even more than in Los Angeles, including Beverly Hills. By best and most recent count, a total of 350 practicing specialists plus another hundred or so in research and administrative jobs with Government. Why so many?

An article which I wrote for the February issue of *The Washingtonian* explores some of the reasons. One is gravitation—the city's attractiveness to the professional practitioner. There is a magnetic cluster of universities and medical schools here, a major Federal hospital for the mentally ill, a National Institute of Mental Health, exceptional institutions for retarded children, and the Washington headquarters of major organizations in the fields of psychiatry, psychoanalysis and psychology.

But these reasons beg the question. We have so many psychiatrists, at least in part, because of the kind of town we are, and because of what ails us. It is of these things that I should like to talk this afternoon.

Washington is a city of executive tensions. Some of these tensions find their way to the psychiatric couch. We are a city of the upward-mobile, the success-strivers. People who come here, as one veteran psychiatrist told me, are enormously competitive, ambitious people. Some are happy and well adjusted before they arrive, and many stay that way. But others become distressed, emotionally ill. But does Washington make them that way?

It would be a precarious thesis to say flatly that it does. But the experts admit to this much: The Success Itch does take its toll among many who work here. The experts agree on some other points too: Washington has more than its share of alcoholics, and problem-drinking can be traced in many cases to the high-intensity social requirements of Washington life.

Transiency is another culprit, especially among military and diplomatic personnel. Perhaps you have heard of the "Colonel Syndrome." It describes the military officer who leaves the power and eminence of command at some remote military installation to come here and be swallowed up in the brass-hat anonymity of the Pentagon. The transition can be traumatic—from being waited on by orderlies to carrying your own tray in a Pentagon cafeteria line. Similar adjustments confront the officer's wife and children.

Crime in Washington has causes peculiar to the city's life also. One is the appalling poverty of our Inner City. Another is the continuing in-migration of poor rural people who come here inadequately equipped for jobs in a high-skill urban setting. To be poor in Washington is to live frustratingly cheek by jowl with wealth, a condition vividly evident on the frayed edges of Georgetown and Capitol Hill. In those areas one literally finds opulence next door to fatherless families and welfare checks.

Washington's suicide rate is high too—above the national average. Psychiatrists and public health authorities see a strong connection between suicide and alcoholism. Why? Because the suicide often is a depressed alcoholic searching for ultimate release from his problems.

A gloomy picture? In many ways it is. But the fact that we have so many psychiatrists, analysts, and facilities for treating the emotionally sick lends brighter hues to the scene. At least in Washington the sick can get help from the private practitioner, the public clinic, in psychiatric units of a half dozen hospitals, and from many lay organizations specializing in group therapy.

Three new, comprehensive neighborhood mental health centers are planned for Washington. They will boost available facilities even higher. Meanwhile, psychiatric consultation is available in 12 foreign languages, and you can even get emotional first aid by telephone, by dialing the number of the city's new Mental Health Consultation and Information Center. Top off all of this with the Federal Government's cordial regard for psychiatry as a method for treating the worker who be-

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* Address before the Zonta Club of Washington, D. C., March 9, 1966.

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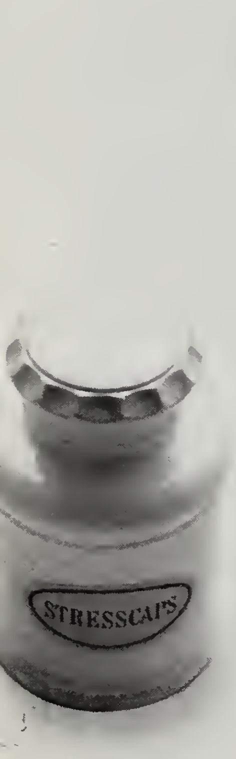

comes emotionally upset and you can see why the picture really isn't so bleak.

Some, of course, would challenge the inventory I have just given you; they might question the claim that the city is well equipped to treat the emotionally and mentally distressed. One of the most outspoken critics is Mike Gorman, Director of the National Committee Against Mental Illness. He says that while Washington has a good many doctors to treat residents in upper- and middle-income groups, personnel and facilities for the care of our lower-income residents are far from adequate. Not enough poor people, he argues, can get into clinics, and none can afford the usual rates charged for a 50-minute hour.

But what about the tensions of Washington life—those emotional disorders with a uniquely Washington aspect? Here are a few tensions supported by evidence in the case notes of a dozen local psychiatrists. Washington is a mecca for the so-called true paranoid, the tormented individual who, in his feelings of persecution, casts about for an authority figure against which to rail or toward which to turn for sympathy. Government fits this description pretty well, for you just can't hardly top Government when it comes to authority figures. It is for this reason that our police and the Secret Service maintain a keen if routine alert for the people who "simply must see the President" and the protesters who, if the picket lines don't suffice, decide to crash the White House gate or write a threatening letter to a Federal official.

You know of such cases. They make headlines. What you have probably heard less about are the garden-variety neurotics, schizophrenics, and paranoids who are in our midst every day leading lives of not-so-quiet desperation. Their suffering, while less spectacular, is no less real. They make up the bulk of the patients seen by psychiatrists who practice in the city and its suburbs: Government workers, Government officials, members of Congress, executives of business firms, housewives, scientists, officers of the military branches, teenagers, small children—in short, an unfortunately representative cross-section of the city. Their biggest, most common problems are anxiety and depression, the "common colds" of all psychiatry.

What about job pressures in Washington? Consider the employee of a highly secret Government Agency. There are tensions unique to a job you can't really discuss with a friend or a neighbor next door—the tensions of silence, the tensions of secrecy. Psychiatrists will tell you that it is not uncommon for men and women in the hush-hush agencies to come to them for help. For some, the pressure of silence is simply too great. The agencies recognize the value of psychiatric consultation, and most retain psychiatrists to treat their own employees. The patient talks. The doctor listens. Sometimes the problem is one of excessive scrupulosity—the fear of saying too much about the job. Sometimes it is one of fear itself. Working in silence and amid tight restrictions on one's personal life can aggravate latent feelings of persecution or of guilt. The worker begins to feel that people are watching him, checking on him, spying on him. One young woman on the payroll of CIA took to double-bolting her doors and calling the police at all hours. She was certain that a foreign agent had her under surveillance. She sought professional help, was treated, and subsequently shed her fear.

Or the problem may be one of pressure: Exhibit A—the work load of some of our highly placed Government officials, a terrific pace, wall-to-wall crises, living in a fish bowl. If their bodies don't fail, it is hardly surprising if their nerves do. Fortunately, psychiatrists find most people at the top levels of Government smart enough and aware enough to recognize the value of preventive treatment. The typical working Washingtonian, it seems, is a well educated, well paid individual with an excellent verbal facility. He is able to talk out his worries and problems.

Doctors say the cocktail circuit of Washington is one of the chief causes for our high rate of alcoholism—arrests for more than 40,000 cases of drunkenness last year alone, but how many more drinking crises don't reach a police blotter? The endless round of compulsory drinking in the embassy crowd, the Capitol Hill crowd, the association crowd. Some highly motivated careerists, frustrated in their efforts to attain still another rung on the success ladder, turn to drink to assuage their frustrations. It can be a dangerous, self-defeating narcotic, hiding the need for reexamination of self.

We talked about that military officer—the one with the "Colonel Syndrome." Well, what about his wife? Chances are she was a Queen Bee in the social environment of a military community. Junior officers fawned over her. Charity groups sought her help and approval. But when she comes to Washington and settles in split-level obscurity, what of her ego then? It is very likely to be damaged. The Queen Bee discovers that she is just a small buzz in the big Washington hive. One doctor summed it up colorfully: "It is awfully difficult," he said, "to compete with Gwen Cafritz on $25,000 a year."

This same sort of thing goes for State Department personnel and for their families, including the sensitive youngster who never stays put in one place long enough to put down roots.

Some experts note what they call "cultural shock in reverse." This is often seen in the families of the State Department when they are recalled from high living in a foreign post to a much less exotic life in one of our suburbs.

Then there are the thousands of single working women in Washington. Many, of course, are happy and well adjusted. But some are not. Some came here during the War years, seeking the glamour of life in the Capital. There is such glamour, but it can wear thin with the passage of years. As a result, some single women become terribly lonely. They seek the company of other women and, living together, their hopes of marriage fading, they make up a society in their own right—one in which depression and even lesbianism can take hold. The psychiatrists say this same chain of events can be seen in the life of the city's bachelors, although apparently fewer of them wind up on the psychiatric couch.

Washington's large and growing Negro population presents some special psychiatric problems. A few Negro physicians—psychiatrist E. Y. Williams of Howard University, for example—detect an accelerating rate of decomposition in the family life of Negro residents. Religion no longer has the pervasive, binding power it once had in the urban Negro milieu. Mothers work. Fathers are absent. Children get into trouble. Drinking. Crime. Violence. Disease. Remember too that Washington Negroes find themselves conspicuously at stage center in the drama of the Negro Revolution. This is, after all, the Nation's Capital, and people of color constitute more than half of our total numbers. Is it really surprising, then, that the typical Negro tension seen by psychiatrists of Washington is one of intense frustration, of grinding impatience?

So you see, to review Washington from a psychiatric viewpoint is to look at many kinds of people and at many varieties of tension. In aggregate terms there is no aggregate—only people and the always present problems of people who are part of a changing society which some have claimed to be mortally sick. But most psychiatrists are optimists, their profession requiring it. Their mission in this city, as elsewhere, is to modify human behavior, with what tools they have, in order to achieve what Karl Menninger described as "that recognition of the forces within us which constitutes the first step in their control." Our intelligence should be applied to forestalling or repairing damage rather than to devising more ingenious forms of retaliatory destructiveness. Applied to the suffering individual, Menninger wrote, this is the principle of psychiatric therapy; applied to the difficulties of the world, it is a rational educational philosophy. In either case, he added, it is based on hope.

Letters to the Editor

Pediatricians and Hospital Staff Dues

Pediatricians pay an unfairly large amount of hospital staff dues each year.

In a recent survey I made of 81 pediatricians in active private practice, mainly in Montgomery County and the District, it was found that they belong to from 5 to 12 hospital staffs, with an average of 8⅔ hospital staff memberships per pediatrician. Yearly courtesy staff dues range from nothing (at George Washington and Georgetown) to $20 at the Washington Hospital Center. Most hospitals charge from $10 to $15 yearly and this amount is steadily rising.

Our membership on most of these many hospital staffs is only for the privilege of seeing newborns.

Baltimore has a different system. I quote from a letter written by Dr. Alexander Schaffer of that city:

"We do permit pediatricians in Baltimore to care for newborns in the nurseries of our hospitals without being dues-paying, voting members of the active staff. This system just grew up and all the hospital staffs have accepted it without question."

At the May meeting of the Montgomery County Pediatric Society these facts were presented and it was suggested that in each of the 8 hospitals in this area where the above situation applies a meeting of the Chief of Pediatrics with the appropriate hospital committee be arranged in an attempt to find a more equitable solution to this problem.

Very truly yours,
VITA R. JAFFE, M.D.
Chairman, Committee on Hospital Staff Dues, Montgomery County (Maryland) Pediatric Society

Policies and Principles for Developing a Medical Assistance Plan*

The District of Columbia Medical Society is profoundly concerned about the health and medical services to be made available to the indigent and medically indigent of the District of Columbia under the provisions of Title XIX of Public Law 89-97, Social Security Amendments of 1965.

The Society has been critical of the present Medical Assistance Program for the Aged in the District of Columbia since it fails to meet the needs of many marginal-income aged for whom the legislation was intended. Furthermore, the pattern of care provided is often ill suited to the medical requirements, being without coördination and continuity and providing little or no choice of physician, hospital, or other medical care facility. That such deficiencies should be corrected is patently obvious when considering the legislative intent of the Congress in enacting changes to strengthen the former Kerr-Mills Program through Title XIX, Public Law 89-97.

The Society believes that any plan can fulfill its responsibility to the people of the District of Columbia only if it conforms to certain fundamental policies and principles. The Society dedicates itself to the fullest coöperation of its organization and members in developing such a plan so as to assure the highest degree of medical care possible to those persons in the District of Columbia who are eligible for benefits under this law.

The Medical Assistance Plan must be designed and administered in a manner which will make the District a model for other cities and states in the Nation. To this end the Society recommends that the following principles be followed in developing and formulating an appropriate program for the Nation's Capital:

1. All community health and medical care resources should be utilized.

The "single state agency" (the Department of Public Health in D. C.), to which has been assigned the responsibility for the program, should work with the entire medical community in seeking new and more efficient approaches to the provision of health and medical services. This will decrease "competition" for scarce medical services.

2. Professional societies, voluntary health agencies, and health-oriented community organizations as well as appropriate District of Columbia departments and agencies should officially participate in planning the scope, content, and priorities of the program.

3. Eligibility under the plan should relate to medical care needs and the inability to finance the expenses of services to meet those needs.

While it is necessary to define resource limitations for eligibility there should be an "open end" provision to permit financial support for extraordinary care needs. Eligibility restrictions under the current Medical Assistance Program for the Aged (Kerr-Mills) include unrealistic income and resource requirements, impractical relative responsibilities, and limitation of services to those provided by District of Columbia Health and Welfare Departments, effectively excluding the very patients for whom the legislation was intended.

4. Equal availability of services and treatment to all eligible persons should be assured without regard to race, color, or social status.

5. The program developed should provide comprehensive care on a continuing basis, all aspects being coördinated by the patient's individual physician.

The importance of a managing physician to provide such coördination and continuity cannot be overemphasized. Many patients have multiple disease states contributing to their disability, and any attempt to restore and maintain their maximum functional competence seldom succeeds without broad-visioned management. The present fragmented approach, in which there is no direction by a personal physician nor assurance of continuity of care, is professionally unsatisfactory for the patient and economically unsatisfactory for the community.

6. The quality, quantity, and availability of services to the indigent and medically indigent should compare favorably with that available to other persons in the District of Columbia who can afford to pay.

7. The administration of the Medical Assistance Plan should be carried out in a manner which will insure full adherence to the purpose and objectives of the law, including freedom of choice of any qualified and participating physician, hospital, or extended care facility that indicates a willingness to provide such services.

The necessity for the patient to transfer from the care of his personal physician to a community clinic in order to receive financial assistance in meeting his medical care need has in effect excluded many marginal-income aged from the existing Medical Assistance Program for the Aged.

8. Arrangements by the single state agency with other District of Columbia departments and agencies for the provision of services should be subject to the same requirements and controls placed on any vendor of services.

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* Prepared by the Committee on Aging and Public Welfare of the Medical Society of the District of Columbia and approved by its Executive Board.

9. Provision should be made for an impartial, objective review of the administration of the program by appropriate community organizations, including professional societies and voluntary health agencies, on at least an annual basis.

10. The single state agency through the Board of Commissioners should periodically make full and complete reports to the public on all aspects of the Medical Assistance Plan, including number and characteristics of indigent and medically indigent persons served, the nature and cost of services, and such other aspects of the program deemed appropriate.

Health Dept. Notes

Some Recent Health Department Publications

THE D. C. DEPARTMENT of Public Health makes considerable use of printed materials in its efforts to inform and educate the public.

These are developed by the Department's publications production staff, working with and on behalf of the various public health and clinical programs. They are intended to explain, describe, and give support to departmental programs, especially those which require public understanding and acceptance.

One such publication, recently distributed to Washington physicians and others, is titled the "Potomac, People and Pollution." This is a pictorial review of the River, its early and present status as a waterway, the nature and scope of such problems as silting and pollution, and the pressing need for controls before the situation becomes irreversible.

The health hazards of water pollution should make this of interest to physicians. The Washington area is dependent on the Potomac for its drinking and household water, and anything which affects the River is therefore potentially a threat to health.

Another recent Department publication is a folder on weight control, foods and nutrition. This was prepared with the aid of nutritionists in the Department of Public Health for use in public clinics and elsewhere. It points out that eating proper foods is essential to weight control and lists certain items which are necessary for good nutrition; it further indicates that persons who have a weight problem should see their family doctor.

Current interest in alcoholism and new awareness that alcoholics are ill have led to the production of a small, attractive folder on this condition. The folder is intended for the known or potential alcoholic. It states that "alcoholism is a treatable illness," mentions some of the symptoms, which the alcoholic might recognize, and lists places in the District where help is obtainable. The latter include the private physicians, the clergy, and public and private agencies.

The folder also gives answers to questions which experience has shown the alcoholic will ask. This includes the nature of treatment, the possibility of being "cured," and the need for family assistance and job security once treatment as an alcoholic is begun. The folder's theme is that alcoholism may seem to be a maze to the person trapped within it, but with understanding professional help there can be escape and return to health.

A small booklet, "You Can Keep Them Safe," was produced earlier this year for distribution to the general public. It shows, with photographs, the kinds of accidents which can occur to very young children in the home and describes ways of avoiding these all too common hazards. This has been a popular, inexpensive publication which is now in its second printing.

Another current publication, intended for more limited distribution, is the "Guide to Services and Facilities for Older Persons" in the District of Columbia. This is a comprehensive directory of hospitals, clinics, nursing and personal care homes, residences, recreational and social programs, visiting nurse and health services, and other public and private agencies offering service to the elderly resident.

It was prepared through the Department's project for improvement of nursing homes, but its uses go well beyond this initial purpose. The guide locates each service and facility and describes the nature of the services it offers.

Physicians may also be interested in the Department's illustrated annual report, "Eyewitness to Public Health," a review of the year's activities in public health in D. C. This comments on community mental health, care for the elderly, maternal and infant health, construction at D. C. General, communicable disease control, and other highlight activities.

Copies of these and other Department publications are offered to the practicing physician in Washington for his own use or for his use with patients. Information about them, including a list of available titles and topics, may be obtained from the Health Education and Information Division, 451 Indiana Avenue, N.W., Washington, D.C. 20001.

MURRAY GRANT, M.D., D.P.H.
D. C. Director of Public Health

President's Committee on Employment of the Handicapped

Report of April 1966 Meeting

The President's Committee on Employment of the Handicapped met in Washington, D. C., April 28 and 29, 1966 for its annual meeting. On Thursday the 28th, Harold Russell, Chairman of the Committee, opened the meeting, presenting a challenge to the participants to continue their outstanding work. He stressed the need for "stronger grass root community support" of "hiring the handicapped" program. He also stressed the need for more voluntary community committees on Employment of the Handicapped.

The Honorable John T. Connor, Secretary of Commerce, gave the keynote address, speaking of the handicapped as "specially able people of the community" or an untapped resource both for Government and industry.

Walter Cronkite gave "A Tribute to Courage" to the handicapped American of the year. This year's award was presented to Robert J. Smithdas, Associate Director of the Industrial Home for the Blind, of Brooklyn, New York. Mr. Smithdas is both blind and deaf. In spite of this overwhelming handicap he obtained a bachelor's and a master's degree. Vice President Hubert H. Humphrey presented the award, congratulating him as an inspiration for both the sighted and unsighted. Mr. Smithdas responded to Mr. Humphrey's remark with a speech of thanks, carefully enunciated, completely audible and well spoken. This was the high point of the meeting to many people. The 5 winners of the "Ability Counts" essay contest were then given awards. Prize-winners were flown to Washington under the sponsorship of AFL-CIO.

There were many workshops. One discussion revolved around the funds now available through War on Poverty that would make it possible for handicapped people to be trained for jobs in Government and civilian work. Vocational Rehabilitation Administration reported that funds have been obtained to train or retrain the handicapped so that they would be able to handle a job. Vocational Rehabilitation Administration in the District of Columbia is now making attempts to obtain funds to implement this opportunity through United Planning Organization. It was pointed out, however, that changes will have to be made in the Workmen's Compensation laws to protect both the employer and the handicapped employee before many businesses could or would hire the trained handicapped.

In addition, electronic equipment was described that eventually might make it possible for a seriously handicapped individual to function independently. Battery-operated prostheses were demonstrated by a group of researchers from the University of Pennsylvania. The equipment is still in the developmental stage but eventually should be helpful to the amputee. An automated wheelchair with a voice unit was demonstrated with a quadriplegic as the demonstrator. This voice-controlled automated wheelchair made it possible for one completely involved quadriplegic person to attend pre-law school and hopefully in the future he will contribute to the community.

Margaret M. Kenrick, M.D.
Member, Committee on Rehabilitation and Chronic Illness, The Medical Society of the District of Columbia

Donors of Furnishings

The Medical Society's House and Building Fund Committee wishes to acknowledge with thanks the following additional donations to funds for the purchase of furnishings for the Society's new building. The original list of donors appeared in the May issue of the Annals; as donations are received they will be acknowledged in future issues.

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Organizations

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In Memoriam

Dr. Raymond T. Holden, Sr. and Mrs. Holden, by Dr. Raymond T. Holden
Dr. Oscar B. Hunter, Sr., by the Oscar B. Hunter Memorial Foundation

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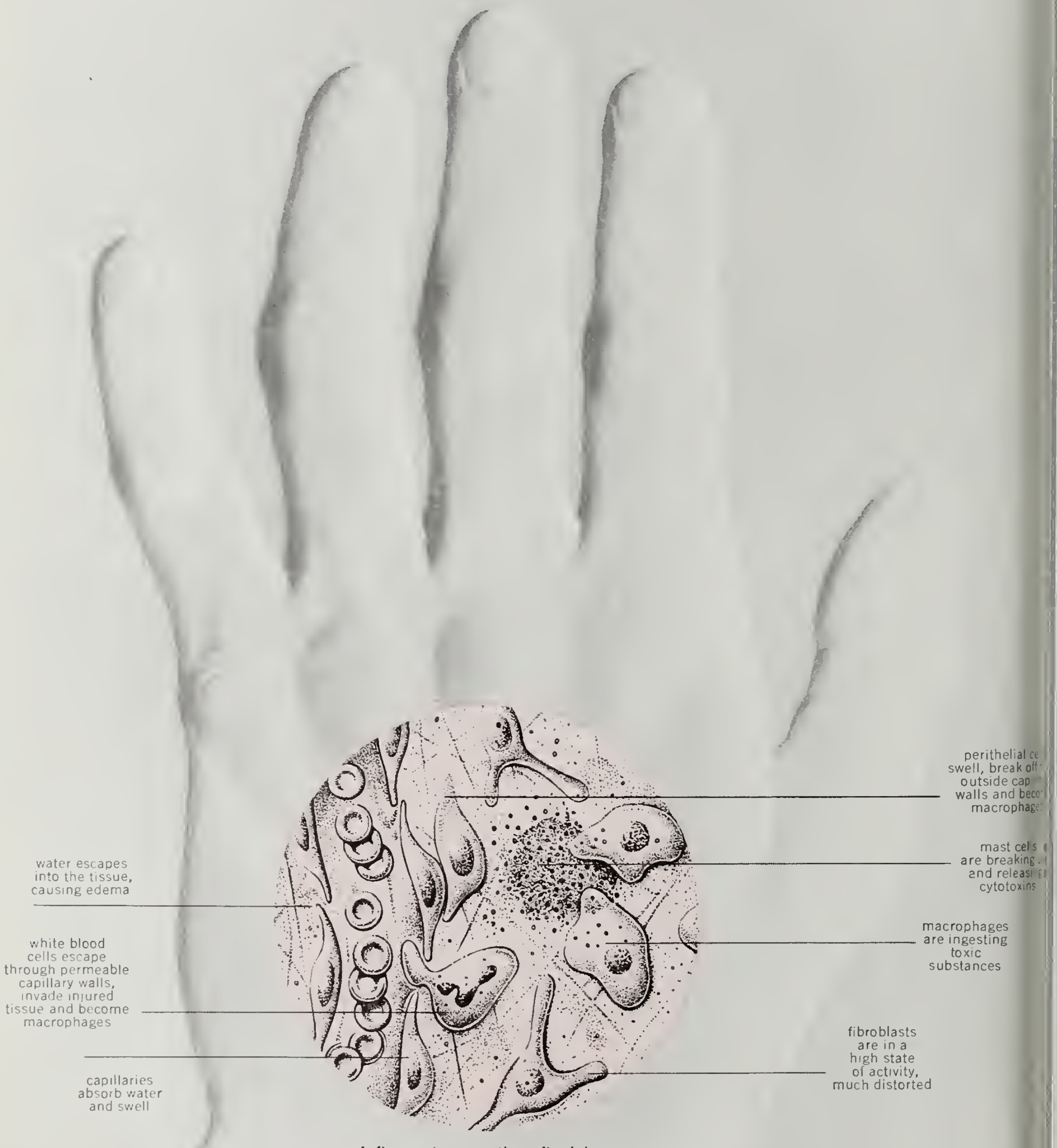
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References: 1. Kanee, B.: Canad Med Ass J 88:999 (May 18) 1963. 2. Scholtz, J. R.: Calif Med 95:224 (Oct.) 1961. 3. Jansen, G. T., Dillaha, C. J., and Honeycutt, W. M.: Arch Derm 92:283 (Sept.) 1965.

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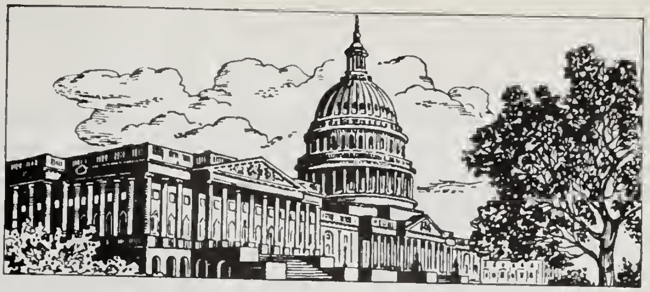

NEWS & PERSONALS

Meetings

A training course, "Control of Infections in Hospitals," will be presented in the Exhibit Hall of the Medical Society of the District of Columbia at 2007 Eye Street, N.W., October 11 and 12, 1966. This course is designed for personnel from national, state, local, religious, military, and private hospitals and institutions.

Dr. Monroe J. Romansky, Professor of Medicine at George Washington University School of Medicine, will moderate the first morning session. Speakers on the first day will be Bernard A Brown, D.V.M., of the Communicable Disease Center, Atlanta, Ga.; Dr. Jay P. Sanford, Professor of Internal Medicine, Southwestern Medical School, The University of Texas; Wilbur R. Taylor, Assistant Chief, Architectural and Engineering Equipment Branch, Division of Hospitals and Medical Facilities, Public Health Service, Washington, D. C.; and George F. Mallison, Chief of the Biophysics Section, Technology Branch, Communicable Disease Center, Atlanta, Ga.

Dr. Clifton K. Himmelsbach, Chairman of the Committee on Infections within Hospitals, American Hospital Association, and Associate Dean for Research, Georgetown University School of Medicine, will be the first speaker at the morning session, Wednesday, October 12; his subject, "Measures for Control of Infections." Other second-day speakers will be Dr. Theodore C. Eickhoff, Acting Chief, Investigations Section, Epidemiology Branch, Communicable Disease Center, Atlanta, Ga.; John F. Horty, LL.B., Director of the Health Law Center, Graduate School of Public Health, University of Pittsburgh; and a panel of 3 physicians and 1 nurse who will discuss "Employee Motivation to Control Infections."

The planning group has been made up of representatives of the D. C. Department of Public Health, the Medical Society of D. C., the Medico-Chirurgical Society of D. C., the Maryland-D. C.-Delaware Hospital Association, Georgetown University School of Medicine, George Washington University School of Medicine, Howard University College of Medicine, the U. S. Department of Health, Education, and Welfare, and other Federal Agencies and hospitals.

The Maryland-D. C. Society of Anesthesiologists, Inc. will hold its Annual Meeting on Sunday, September 18, at the National Naval Medical Center in Bethesda, Md. Commander R. J. Van Houten, MC, USN, President of the Society of Military Anesthesiologists, will host the meeting.

A short business meeting at 1:30 p.m. will be followed by a scientific session at 2:00 p.m. "Practical Pulmonary Physiology" will be the subject for discussion. Panelists, all from the staff of the Veterans Administration Hospital, Washington, will be Dr. Sol Katz, Chief of Medical Service; Dr. Peter C. Luchsinger, Chief of the Cardiopulmonary Physiology Research; Dr. Hall G. Canter, Assistant Chief of Medical Service; and Dr. Donald P. Schilder, Director of the Emphysema Unit.

Wives and husbands are cordially invited to join members for cocktails in the early evening and at the dinner to follow. Reservations should be made with Dr. Mary Lou Barker at 5609 Bent Branch Road, Washington, D. C. 20016.

The III International Congress of Nephrology will convene this month at the Washington Hilton Hotel, September 25–30. At the Opening Plenary Session, Sunday evening, September 25, officials of the United States Government and officers of the Congress will welcome members and affiliate members. The first General Session will open on Monday, September 26, at 9:30 a.m. General sessions and symposia along with sessions of free communications will offer summaries of recent advances and work in progress in the major areas of research on the kidney. To facilitate communication, 3-language simultaneous translation will be provided for all general sessions and some symposia.

Dr. George E. Schreiner, Secretary-General of the Congress, will address the general session, Tuesday morning, on "Problems of Chronic Dialysis."

There will be 1-day scientific registration of $12.00 and a special 1-day registration for members of hospital house staffs, residents and fellows of $5.00. Registration forms and additional information are available at the Secretariat, 9650 Wisconsin Avenue, Washington, D. C. 20014.

A program of Postgraduate Medical Education will be presented at the **Veterans Administration Hospital**, 50 Irving Street, N. W., each Thursday afternoon beginning September 29, 1966 and continuing until June 22, 1967.

From 1:30 to 2:30 p.m. there will be a Combined Clinical Conference where significant clinical problems involving various specialties will be discussed in detail.

Weekly sessions relating to "Latest Developments in Medicine" will be presented from 3:00 to 4:30 p.m. They will consist of a series of topics, over a number of weeks, each topic under the directorship of a qualified member of the Hospital staff.

The first topic, on Medical Genetics, will continue from September 29 through November 10. These 7 sessions will be under the direction of Kenneth L. Becker, M.D., Ph.D., Chief of the Section of Metabolism and Genetics and Assistant Professor of Medicine, George Washington University School of Medicine. The speakers and topics to be discussed are as follows:

September 29: "Pedigree Analysis." Dr. Becker
October 6: "Molecular Basis of Genetics." Dr. S. H. Boyer IV, Associate Professor of Medicine, Johns Hopkins University School of Medicine
October 13: "Chromosomal Medicine." Dr. Kurt Hirschhorn, Associate Professor of Medicine, New York University School of Medicine
October 20: "Heritable Disorders of Connective Tissue." Dr. Victor A. McKusick, Professor of Medicine and Chief, Division of Medical Genetics, Johns Hopkins University School of Medicine
October 27: "Clinical Aspects of Abnormal Hemoglobins." Dr. Paul Heller, Associate Chief of Staff for Research and Chief of Hematology Section, Veterans Administration West Side Hospital, Chicago
November 3: "Inborn Errors of Metabolism." Dr. R. Rodney Howell, Associate Professor of Pediatrics, Johns Hopkins University School of Medicine
November 10: "Population Genetics." Dr. McKusick.

Both of these series will be held in the Hospital theater on the fourth floor. Coffee and refreshments will be served between the 2 sessions.

All physicians and medical students are cordially invited to attend.

The 51st Annual Scientific Assembly of the Interstate Postgraduate Medical Association will convene in Washington, D. C., October 17–20, at the Sheraton-Park Hotel. Many members of the D. C. Medical Society will participate in the program and there will be prominent out-of-town speakers each day.

A special feature of the meeting is the Scientific Noon Luncheon Conferences, 10 each day, Monday, Tuesday and Wednesday. Attendance is limited to 80 per luncheon, so advance reservations are advised. Members of the Medical Society who will lead luncheon discussions are (Monday) Drs. Dale C. Cameron, Robert J. Coffey, Robert S. Higdon, Roland B. Scott, Harold Stevens, Leon Yochelson; (Tuesday) Brian Blades, Edward D. Freis, William S. McCune, John C. Rose; (Wednesday) Robert H. Barter, Thomas McP. Brown, and Thomas W. Mattingly.

Monday, October 17: Dr. Coffey will moderate an Orthopedic Clinic in which Dr. John P. Adams will discuss "Foot Problems" and Dr. George W. Hyatt, "Back Problems." Papers on Monday will include one by Dr. Sol Katz on "Emphysema—Our Most Crippling Disease." In the evening Dr. W. Proctor Harvey will head a Clinical Cardiology Conference and Dr. Yochelson will conduct a clinic on "Psychiatric Principles in Medical Interviewing."

Tuesday, October 18: Dr. Joseph F. Sadusk, Jr., will moderate a Panel on Drug Therapy, with Dr. Freis as a discussant on "The Hypertensive Drugs." In a Symposium on "The Severely Injured Patient" Dr. James Peter Murphy will discuss "Head and Neck Injuries." In the evening there will be 2 hours of medical motion pictures.

Wednesday, October 19: Dr. John L. Parks, who is President of the Association, will speak on "Gynecologic Care of Postmenopausal Patients." The other speakers on Wednesday will be from out of town. At the Annual Dinner in the evening Dr. Walter H. Judd, former Congressman from Minnesota, will be the featured speaker; his subject, "Where in the World Are We Going?"

Thursday, October 20: Drs. Brown, Irene G. Tamagna and Charles S. Wise will conduct a clinic on "Rehabilitation of the Stroke Patient." Dr. Janet G. Travell, the concluding speaker on Thursday, will discuss "Special Aspects of the Management of Musculoskeletal Pain." The Assembly will adjourn at noon.

The program is acceptable for 18 accredited hours by the American Academy of General Practice. Full details can be secured by writing to Dr. Alton Ochsner, Program Chairman, IPMA, Box 1109, Madison, Wis. 53701.

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1. Riese, J. A.: Amer. J. Gastroent. 28:541 (Nov.) 1957

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General News

Dr. Charles L. Hudson of Cleveland, Ohio, took office as the **121st President of the American Medical Association**, June 28, during the Annual Convention, June 26–30. **Dr. Milford O. Rouse**, of Dallas, Texas, is the **new President-elect**. Speaker of the House since 1963, he will take office next June at the Annual Convention.

Dr. Wesley W. Hall, of Reno, Nevada, was elected Chairman of the Board of Trustees of the AMA, succeeding Dr. Percy E. Hopkins, who did not seek reëlection.

The AMA Distinguished Service Award for 1966 went to Dr. Warren H. Cole, of Chicago. Dr. Cole is Professor of Surgery and head of the Department of Surgery at the University of Illinois College of Medicine. Dr. John T. Edsall received the $5,000 Passano Foundation Award for 1966. He is Professor of Biological Chemistry at Harvard University.

The recent Convention marked the inauguration of a new means of mass communication to the medical profession—the National Science Network broadcast of 15-minute programs called "Doctors Convention Report," in 3 major cities, twice daily. This was the first time that broadcasting, intended for physicians only, was done on an open FM channel. The programs, sponsored by the Ciba Pharmaceutical Company of Summit, N. J., were prepared and presented in Chicago by Dr. Leonard Lewis. The tapes were then flown to KFMU in Los Angeles and WNCN in New York so that they could be heard the same evening and repeated the next morning.

Total registration for the AMA meeting in Chicago was 35,506. This included 12,445 physicians.

The Society for Cryo-ophthalmology has been formed to promote investigative and clinical applications of low-temperature techniques to the eye. Dr. John G. Bellows, 30 North Michigan Blvd., Chicago, Ill. 60602 will welcome applications for membership from those interested in the investigative aspects of this subject, the preservation of ocular tissue, therapeutic applications of cryogenics to various ocular diseases, and cryosurgical techniques. It is contemplated that scientific meetings will be held immediately prior to the annual sessions of the American Academy of Ophthalmology and Otolaryngology.

Children's Hospital Research Foundation of the District of Columbia is the recipient of a $165,300 contract from the National Institute of Child Health and Human Development to conduct research on what is called the "sudden infant death syndrome." This term is applied to approximately 10,000 to 20,000 deaths of American babies annually, including an estimated 150 in the Washington Metropolitan Area. "Sudden infant death" comes to apparently healthy babies, usually between 2 and 4 months of age, but may strike at any time between birth and 2 years of age.

Dr. James Patrick, Chief Pathologist at Children's Hospital, will head the research team conducting the 1-year study. Other team members will include experts in virology and epidemiology.

Mr. Matthew F. McNulty, Jr., has been granted a leave of absence from the University of Alabama **to establish the Council of University Teaching Hospitals** of the American Association of Medical Colleges in Washington, D. C. As Director of the Council, Mr. McNulty will be responsible for developing a program and an organization to represent the voice and opinion of the 300 major teaching hospitals in the United States, Canada and Mexico. Mr. McNulty is General Director of the University of Alabama Hospitals and Clinics. He was recently appointed Dean of the new University of Alabama School of Health Services Administration.

On July 18 the **Albert Deutsch Center** at 1816 19th Street, N.W. began its operation of a rehabilitation program for adults recovering from emotional illness. Designed to bridge the gap from social isolation to more active community participation, the Center will provide an opportunity to engage in vocational guidance and training, home arts instruction, social and recreational activities, and group and individual counseling.

Referrals will be welcomed from agencies and physicians working with the mentally ill. Inquiries and referrals can be made by calling 332–7731. An informal visit to the Center before referral might be helpful in determining appropriate candidates for the program.

The Center will be open from 9 a.m. to 4 p.m., Monday through Thursday, and 9 a.m. to 10 p.m. Fridays; evening hours will be expanded as membership needs are determined.

The D. C. Association for Mental Health is sponsoring the project in coöperation with the D. C. Department of Vocational Rehabilitation.

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Miss Susannah Hall is Director of the Center and Mr. John K. Clagett, Assistant to the Director. Volunteers will participate in all phases of the operation.

The U. S. Public Health Service has awarded **a cancer training grant to Children's Hospital** to help support establishment of a complete cancer center for children which will serve the Washington Metropolitan Area and nearby states.

Dr. Sanford L. Leikin, Director of Hematology at Children's Hospital, has been named Director of the project. He has long been active in pediatric cancer research and treatment.

The $33,000 annual grant, awarded for a period of 3 years, is the first to be designated by the Public Health Service for the specific training of practicing physicians, medical studients, and nurses in the latest techniques of detecting and treating cancer in youngsters.

Two new publications, **"Chronic Respiratory Diseases, A Growing Menace" and "Management of Chronic Obstructive Respiratory Diseases,"** have been released by the U. S. Public Health Service. The first, publication no. 1445, describes the increasing significance of these diseases and outlines the functions and activities of the new PHS control program. The second, on management of respiratory diseases (PHS publication no. 1457) is a résumé of the Eighth Annual Emphysema Conference held in Aspen, Colorado, in June 1965.

Both of these publications are being mailed to physicians throughout the country. In addition, single copies are available from PHS, Department of Health, Education, and Welfare, Washington, D. C. 20201. Booklets in quantity may be purchased from the Superintendent of Documents.

The Section on Ophthalmology of the Medical Society of the District of Columbia has elected new officers. They are:

Dr. L. Edward Perraut, *Chairman*; Dr. Melvin G. Alper, *Vice Chairman;* Dr. H. William Gray, *Secretary-Treasurer;* Drs. Dan G. Albert and John W. McTigue, *members of the Executive Committee.*

Mr. Chester L. Watts, former administrative assistant on the executive staff of the American Academy of General Practice, has been **named Executive Director of the Medic Alert Foundation International** of Turlock, California.

Personals

The appointment of **Lt. General Lenonard D. Heaton** as Surgeon General of the Army has been extended by President Johnson to December 1. 1968. This marks the third time General Heaton's tour as the Surgeon General has been extended since he assumed office in June 1959. General Heaton is an Honorary member of the D. C. Medical Society.

Dr. Henry P. Laughlin, of Bethesda, Md., an Associate member of the D. C. Medical Society, received the annual Alumni Award from Ursinus College in Collegeville, Pa., June 4. The award recognizes "scholarship, dedication, and devoted service to Ursinus College over the years."

Dr. Edward J. Jahnke, Jr. and Dr. Paul G. Rhodes were admitted as new Fellows of the American College of Chest Physicians during the recent 32nd Annual Meeting of the College in Chicago, June 24–27.

Dr. William D. Terrell, Jr. was recently elected a Fellow of the American College of Obstetricians and Gynecologists.

Obituaries

Morris Silverman, A.B., M.D.

(1907–1966)

Dr. Morris Silverman, Washington radiologist, died at the Washington Hospital Center, May 30, 1966.

Dr. Silverman was born in New York City, July 2, 1907 to Jacob and Bessie Kogod Silverman. He graduated from Eastern High School in Washington and from George Washington University, receiving his A.B. degree in 1929 and his medical degree in 1933.

He interned at Gallinger Municipal (now D. C. General) Hospital for a year and then spent a year on active duty with the U. S. Army as First Lieutenant in the Medical Reserve Corps. After a year's residency at the Chesapeake and Ohio Hospital in Huntington, W. Va., he began training in his special interest, radiology, spending a

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year at Beth Israel Hospital in New York City and 2 years, 1939–41, at Kings County Hospital in Brooklyn, N. Y.

He served as Captain in the Medical Corps of the U. S. Army from 1942 to 1943, then was commissioned to active duty in the Reserve Corps of the United States Public Health Service, from 1943 to 1945. In 1945 he was appointed Chief of the Department of Roentgenology at the Washington Regional Office of the Veterans Administration. Ten years later (1955) he resigned this position to become roentgenologist to the Tuberculosis Control Division of the D. C. Health Department. He was consulting radiologist to the U. S. Public Health Service. He also maintained a private practice in offices at 2025 Eye Street, N.W.

Dr. Silverman was certified by the American Board of Radiology. He was an Active member of the Medical Society of the District of Columbia, a Fellow of the American College of Radiology, and a member of the Jacobi Medical Society.

Surviving him are his wife, Mrs. Helen Kaplan Silverman, and a daughter, Frances, both of the home address, 6332 31st Place, N.W. He also leaves another daughter, Mrs. Stephan Gallin, of 8601 Manchester Road, Silver Spring, Md.; a sister, Mrs. Lester Tepper, of Chevy Chase, Md.; and a brother, Irvin Silverman, of Washington, D. C.

John William DuChez, M.D.

(1920–1966)

Dr. John W. DuChez, specialist in internal medicine, died, June 5, 1966, at his home in Springfield, Md. His offices were at 2015 R Street, N.W.

Dr. DuChez was born in Denver, Colorado, April 3, 1920 to John C. and Rose Belle DuChez. He attended Western Reserve University and graduated in medicine from George Washington University in 1943.

With World War II in progress, he enlisted in the United States Navy. After interning for a year at the U. S. Naval Hospital in New Orleans, which is affiliated with the Southern Baptist Hospital, he served as Navy Lieutenant in the Pacific Area until 1947. After the War he took postgraduate training in internal medicine, serving as a resident physician for a year each at Gallinger Municipal (now D. C. General) Hospital and the George Washington University Hospital. He began private practice in his field in Washington in July 1949; his special interest was hypertension.

Dr. DuChez was Associate Clinical Professor of Medicine at George Washington University School of Medicine. He served on the staffs of the University Hospital and D. C. General Hospital, and was senior advisor in internal medicine to the Office of Medical Services of the Central Intelligence Agency.

He was an Active member of the Medical Society of the District of Columbia since 1950 and a member of the Washington Heart Association, the Louis Mackall Society, and the George Washington University Medical Alumni Association. He belonged to the Kenwood Golf and Country Club.

Surviving him are his wife, Mrs. Mary DuChez, and 2 sons, John and Gordon, all of the home address, 5503 Newington Road, Springfield, Md. A sister, Mrs. Donald Nellins, resides at Waukegan, Ill.

Rhegmatogenous Retinal Detachment—
Pilkerton and O'Rourke

(Continued from page 485)

inability of the choroid to absorb the subretinal fluid or by the large size and number of the retinal breaks. In any case, when the retinal detachment or the size and number of breaks increase in spite of strict bed rest, the prognosis is poor with nonbuckling procedures. Light coagulation and laser techniques are only effective when the retinal break is not detached.[3]

One cannot overemphasize the importance of early diagnosis and treatment of detachment. Operation before the macula is involved is important for preservation of good central visual acuity. When the macula is detached immediate operation is important to salvage as much central vision as possible and to avoid fixed folds and massive preretinal retraction. The surgical prognosis in early cases is nearly always excellent.

References

1. McMeel, J. W.: Conference notes.
2. Pischel, D. K., editor: Symposium: Present status of retinal detachment surgery. Trans. Amer. Acad. Ophthal. Otolaryng., 1964, **68,** 919.
3. Schepens, C., and Regan, C.: Controversial Aspects of the Management of Retinal Detachment. Boston: Little, 1965.

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COMPOSITION: Imferon (iron dextran injection) is a well-tolerated solution of iron dextran complex providing an equivalent of 50 mg. in each cc. The solution contains 0.9% sodium chloride and has a pH of 5.2-6.0. The 10 cc. vial contains 0.5% phenol as a preservative.
ADMINISTRATION AND DOSAGE: Dosage, based upon body weight and Gm. Hb/100 cc. of blood, ranges from 0.5 cc. in infants to 5.0 cc. in adults, daily, every other day, or weekly. Initial test doses are advisable. The total iron requirement for the individual patient is readily obtainable from the dosage chart in the package insert. Deep intramuscular injection in the upper outer quadrant of the buttock, using a Z-track technique, (with displacement of the skin laterally prior to injection), insures absorption and will help avoid staining of the skin. A 2-inch needle is recommended for the adult of average size.
SIDE EFFECTS: Local and systemic side effects are few. Staining of the skin may occur. Excessive dosage, beyond the calculated need, may cause hemosiderosis. Although allergic or anaphylatoid reactions are not common, occasional severe reactions have been observed, including three fatal reactions which may have been due to Imferon (iron dextran injection). Urticaria, arthralgia, lymphadenopathy, nausea, headache and fever have occasionally been reported.
PRECAUTIONS: If sensitivity to test doses is manifested, the drug should not be given. Imferon (iron dextran injection) must be administered by deep intramuscular injection only. Inject only in the upper outer quadrant of the buttock, not in the arm or other exposed area.
CONTRAINDICATIONS: Imferon (iron dextran injection) is contraindicated in patients sensitive to iron dextran complex. Since its use is intended for the treatment of iron deficiency anemia only it is contraindicated in other anemias.
CARCINOGENICITY POTENTIAL: Using relatively massive doses. Imferon (iron dextran injection) has been shown to produce sarcoma in rats, mice and rabbits and possibly in hamsters, but not in guinea pigs. The risk of carcinogenesis, if any in man, following recommended therapy with Imferon (iron dextran injection) appears to be extremely small.
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BOOK REVIEWS

Blood Diseases of Infancy and Childhood, 2nd ed. Carl H. Smith, M.A., M.D. Price, $22.00. Pp. 800, with 85 illustrations and 1 in color. St. Louis: Mosby, 1966.

The first edition of this book came out in 1960 and was 572 pages long. It was a most welcomed book because it provided a textbook in which the salient features of blood dyscrasias were presented against the background of normal development of infancy and childhood.

The second and current edition is 800 pages long. The book has been enlarged to include a number of disease entities omitted in the first edition. New information has been added indicating the rapid progress that has taken place in all fields of hematology in the past 6 years.

In particular, this edition covers well the rapid advances made in the study of the causes of hyperbilirubinemia and hemolytic diseases of the newborn. The spectrophotometric examination of amniotic fluid obtained by amniocentesis in the management of the Rh negative mother is mentioned. However, the discussion on amniocentesis is included under laboratory findings in the newborn instead of the fetus—yet, amniocentesis is a test done on the fetus.

The chapter on Hereditary Hemoglobinopathies gives an excellent discussion on hemoglobin chains. It also includes a fine table on Common Abnormal Hemoglobin Syndromes.

The chapter on Coagulation Disorders includes a very good therapy schedule, using fresh frozen plasma, with a good summary of replacement therapy for coagulation disorders.

The close association of genetics and cytogenetics to hematologic disorders has prompted the inclusion of a glossary of chromosomal and genetic terminology.

Throughout, the text is richly illustrated, and extensive bibliographies are found at the end of each chapter.

This is a good book for the pediatric hematologist, the pediatrician, the general practitioner, the house officer, and even the medical student. The present edition, as the previous one, emphasizes the pathogenesis of hematologic disorders of the pediatric age group. It will add to the knowledge of anyone concerned with the care of children. This reviewer found the second edition pleasant, informative, complete, and up to date.

Artemis P. Simopoulos, M.D.

The Role of Psychiatry in Medical Education. An Appraisal and a Forecast. Sidney L. Werkman, M.D. Price, $4.75. Pp. 187. Cambridge, Mass.: Harvard, 1966.

It is the author's intention to critically review the current methods of teaching psychiatry in our medical schools, to point out reasons why most of these programs are inadequate, and to outline for the medical student an ideal curriculum with respect to psychiatry.

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Werkman begins with a review of the development of the teaching of psychiatry at the medical school level since 1933, at which time about 77 hours of the entire curriculum were devoted to psychiatric problems. Since then significant changes have taken place in a number of medical schools. Whereas the Flexner Report emphasized biological sciences, the accent is now shifting toward a wider understanding of human development and of sociological aspects of emotional maladjustment in the broadest sense of the term. In order to accomplish this, family study plans, early confrontation of the student with the patient, psychiatric outpatient care, and closer teamwork between the various medical specialties and the department of psychiatry have been introduced. The rapidly increasing knowledge in such fields as the behavioral sciences, psychophysiology, and psychopharmacology is slowly being integrated into the curriculum.

In the middle section of the book Werkman reports on the findings and experiences he made in a number of medical schools throughout this country. The final part is devoted to an outline of what he considers an ideal teaching program of psychiatry woven into the entire curriculum of the medical student. It is based on the hardly refutable premise that all future physicians need a thorough grounding in psychiatry since, no matter what their specialty may be, a large percentage of their patients will have emotional problems. In addition Werkman sensibly notes that the shortage of psychiatrists limits the type of patients they can treat to those very seriously ill, while a great number of other emotionally sick patients will have to be taken care of by the family physician.

Werkman believes that about 400 hours of the medical curriculum's 4,000 hours should be devoted to psychiatric problems, and that a considerable portion of what is now being taught, or ought to be taught, by the department of psychiatry should be absorbed by the department of preventive medicine, which will have to be expanded considerably.

There can be little argument about Werkman's "ideal program," which is refreshingly free of any particular bias. Of course, real problems will arise with its

(*Continued on page 46*)

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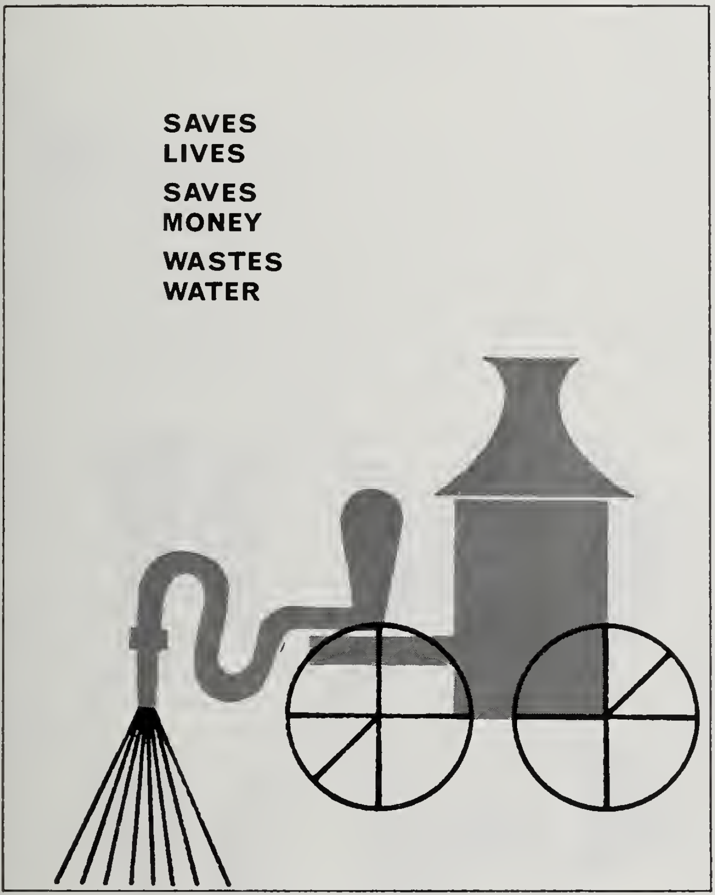

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Side Effects: Nausea, flushing, constipation, skin rash, muscle cramps and gastric discomfort have occasionally been noted; rarely thrombocytopenia and bone marrow depression, photosensitivity, cholestatic jaundice, pancreatitis, perimacular edema, gout and diabetes have been caused by the administration of thiazides.

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Book Reviews

(Continued from page 44)

implementation. Obviously, the already fairly large staff of some of the better psychiatric departments will need further expansion, and other faculties may have to give up some of their time. Finally, in the already intense and highly saturated life of the medical student time will have to be found to absorb the growing knowledge in the field of psychiatry that often is so very different from the material learned in other courses.

To accomplish anything that comes near the "ideal program" will take much time, work and patience. It might be unavoidable, and perhaps even more appropriate to teach some of the more detailed material during internship and nonpsychiatric residencies. However, no matter how much is accomplished in this direction, the ulitmate success will depend on the quality of the teachers and the amount of time they can devote not only to teaching but also to the proper preparation of lectures, seminars or rounds. In this sector, too, much needs to be done.

Werkman's book is written with clarity in style and exposition. It has an abundent list of 105 references and a good index. It presents welcome and useful data and ideas for all those who are involved with teaching and the administration of our medical schools, and it deserves translation into foreign languages.

Felix von Mendelssohn, M.D.

Ciba Foundation Symposium: Complement. Edited by G. E. W. Wolstenholme, O.B.E., F.R.C.P., F.I. Biol., and Julie Knight, B.A. Price, $12.50. Pp. 388 with 50 illustrations. Boston: Little, 1965.

This book is the result of another of a series of small international conferences within the general field of immunology sponsored by the Ciba Foundation. The nature and the manner by which the complement system figures in many protective and destructive effects of antibodies is the main theme discussed by 25 internationally known leading experts in the field. The Symposium is divided into a series of 15 presentations on different aspects of the subject followed by a detailed discussion and critique by the participants.

An authoritative review by Dr. M. Mayer of the present concepts and the nomenclature involved in the mechanism of hemolysis by complement serves as an introduction to the Symposium. There is a thorough presentation of the factors that inhibit and activate complement in vitro. The role of the complement in the mechanism of homograft rejection is discussed in detail. Experimental evidence is introduced to suggest that the action of complement on sensitized nucleated cells is basically similar to its action on sensitized mammalian erythrocytes. The application of electron microscopy to demonstrate the lesions produced in cell membranes of sheep erythrocytes lysed with Forssmann antibody and guinea pig complement reveals characteristic large number of holes on the surface of the membranes. These studies leave little doubt that these holes represent the sites of damage produced by complement.

The difficulties inherent in drawing a clear picture of the role of complement in phagocytosis are well illustrated along with the part played by complement in the complex phenomenon of immune adherence. The known factors about the nature of conglutinins and immunoconglutinins and their relation to complement both in vitro and in vivo are well discussed. The similarity between the autostimulated immunoconglutinins and the rheumatoid factors is implied. The uncertainty regarding the biological significance of complement is stressed with particular reference to its role in host resistance to infectious disease, and its action in autoimmune diseases.

Experimental evidence is presented to show that the mechanism for the increased intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria is due largely to a greater efficiency of the complement complex at the red cell surface.

The Symposium ends with a general discussion by the participants. This consists of a general review of what has been accomplished in the study of complement followed by a delineation of future research.

The book has some excellent black and white photographs, and the experimental results are well illustrated with a generous number of tables. Each presentation is followed by a pertinent list of references.

This book is a must for individuals working in the field of immunology. The pathologist and the internist interested in basic science will find this book stimulating.

Jorge B. Morales, M.D.

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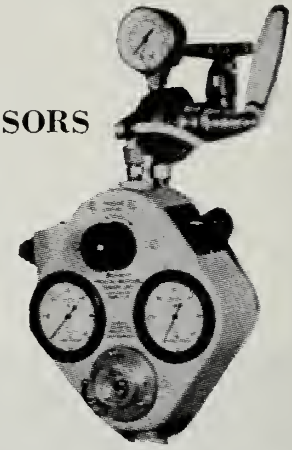

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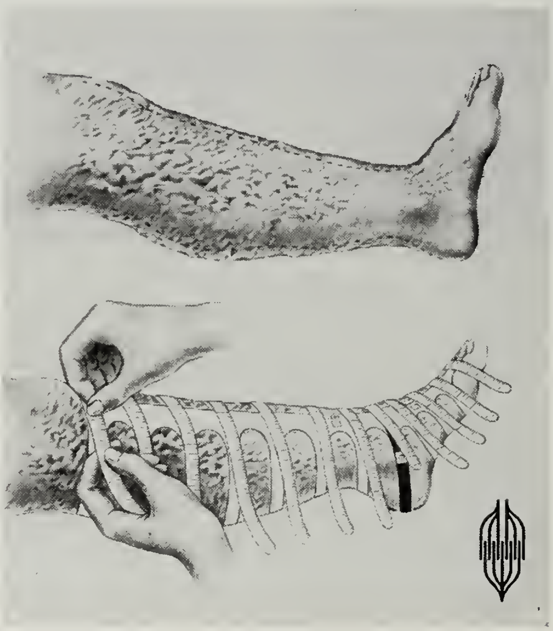

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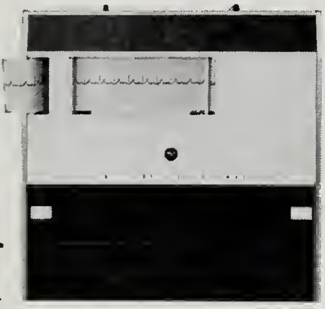

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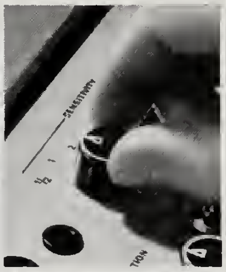

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MOLECULAR REMODELING–

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis—a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect—metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors —in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'—an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase—it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic—an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9, 10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

Naturetin—effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.

Contraindications: Severe renal impairment; previous hypersensitivity.

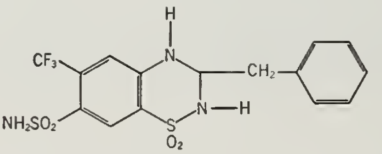
Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

References: **1.** Southworth, H.: Proc. Soc. Exper. Biol. & Med. *36*:58, 1937. **2.** Mann, T. and Keilin, D.: Nature *146*:164, 1940. **3.** Pitts, R. F., and Alexander, R. S.: Am. J. Physiol. *144*:239, 1945. **4.** Schwartz, W. B.: New England J. Med. *240*:173, 1949. **5.** Friedberg, C. K., in Moyer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia, W. B. Saunders Co., 1960, p. 259. **6.** Cumming, J. R.; Tabachnick, E., and Seelig, M., in Moyer, J. H., and Fuchs, M.: op. cit., p. 254. **7.** Werko, L., in Moyer, J. H., and Fuchs, M.: op. cit., p. 188. **8.** Beyer, K. H., Jr., in Moyer, J. H., and Fuchs, M.: op. cit., p. 274. **9.** Maren, T. H., and Wiley, C. E.: J. Pharmacol. & Exper. Therap. *143*:230, 1964. **10.** Earley, L. E., and Orloff, J.: Ann. Rev. Med. *15*:149, 1964. **11.** Fuchs, M., and Mallin, S. R., in Moyer, J. H., and Fuchs, M.: op. cit., p. 276. **12.** Ford, R. V., in Moyer, J. H., and Fuchs, M.: op. cit., p. 290. **13.** cited in Fuchs, M., and Mallin, S. R. (ref. 11): op. cit., p. 283.



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Precautions—Some individuals may experience drowsiness, anorexia, and slight gastric distress. If excessive drowsiness occurs, it may be necessary to increase the interval between doses. Persons on full dosage should not operate any vehicle. Use may result in overgrowth of nonsusceptible organisms. If infections appear during therapy, appropriate measures should be taken. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Infections caused by beta-hemolytic streptococci should be treated for at least 10 full days to help prevent rheumatic fever or acute glomerulonephritis. Use of tetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect has been observed in usual short treatment courses.

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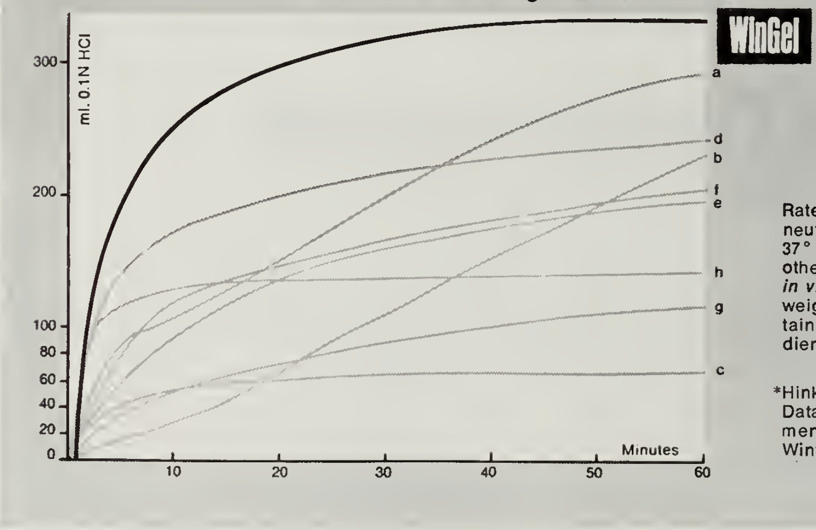

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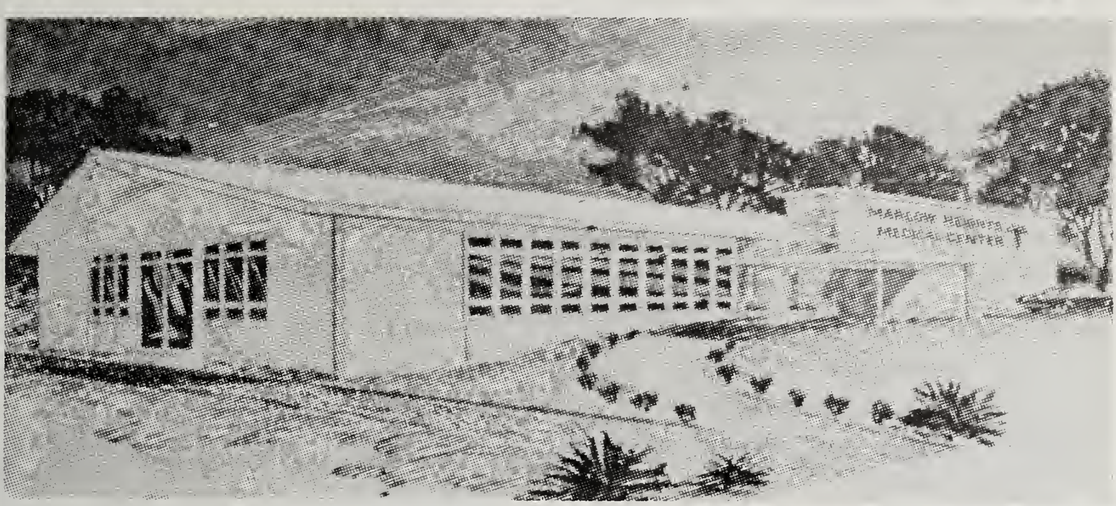
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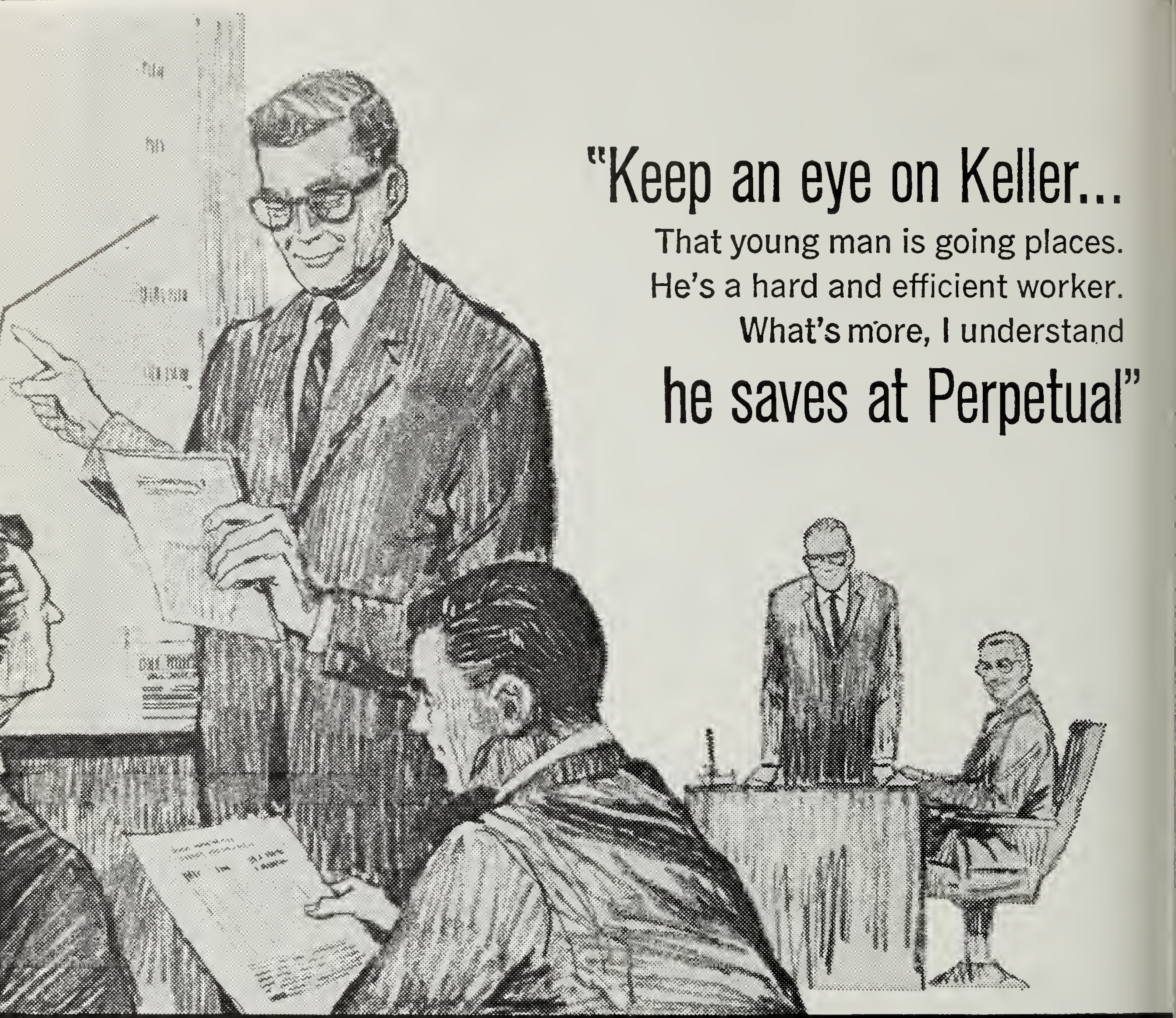
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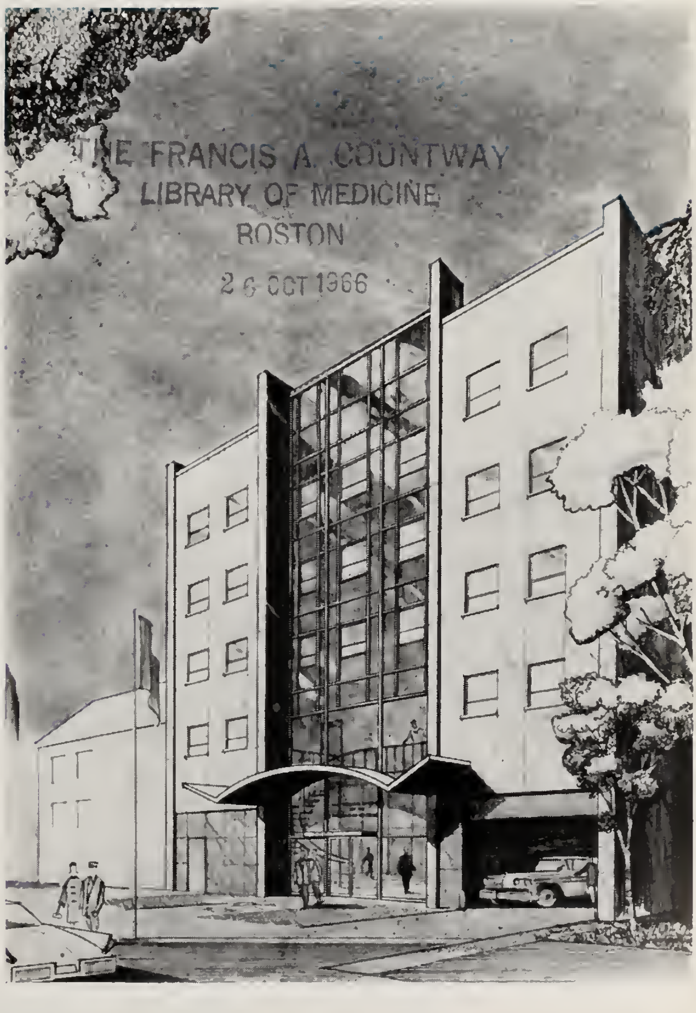

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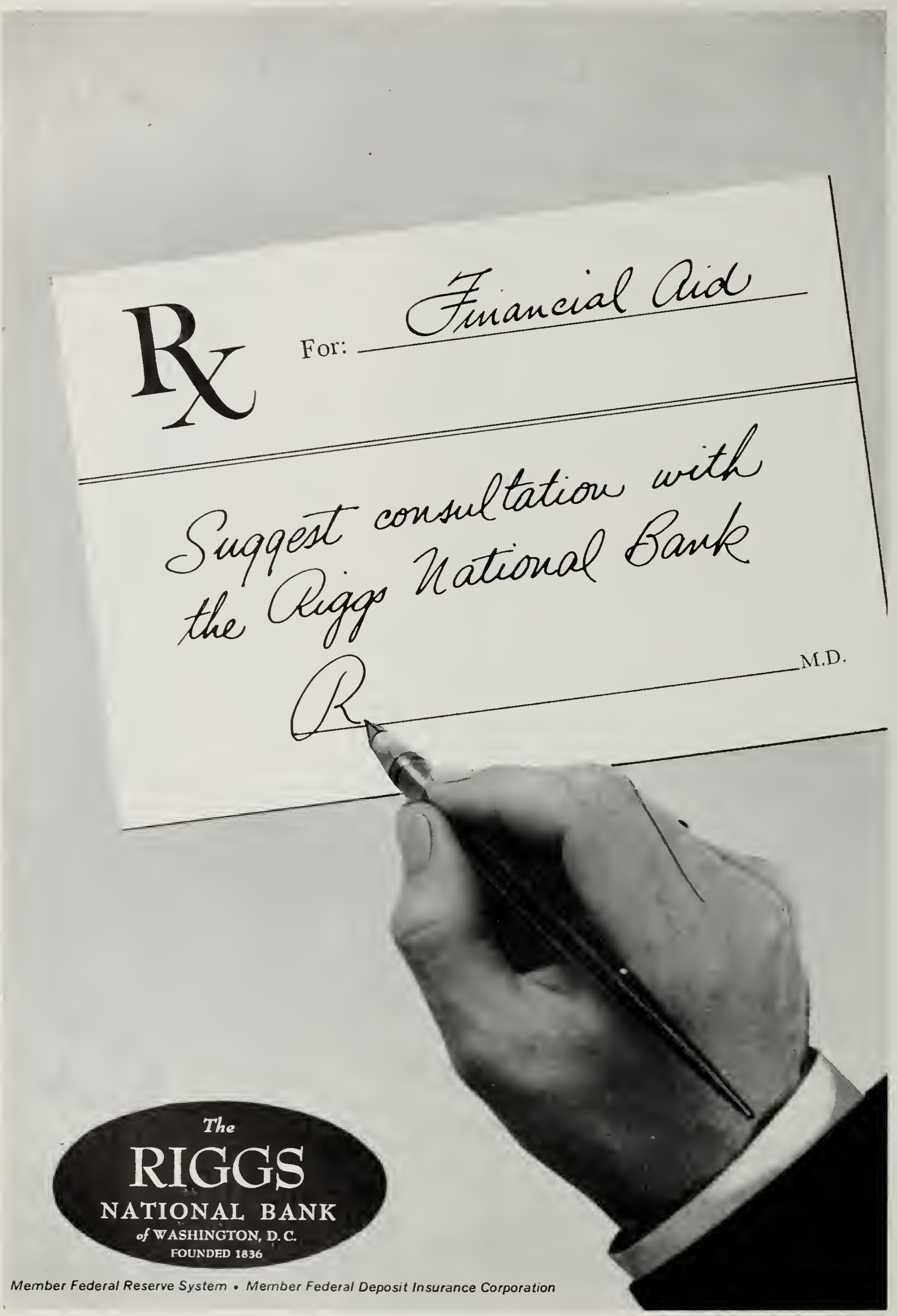
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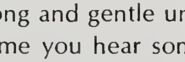

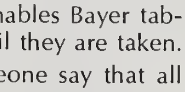

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†The need for these substances in human nutrition has not been established.

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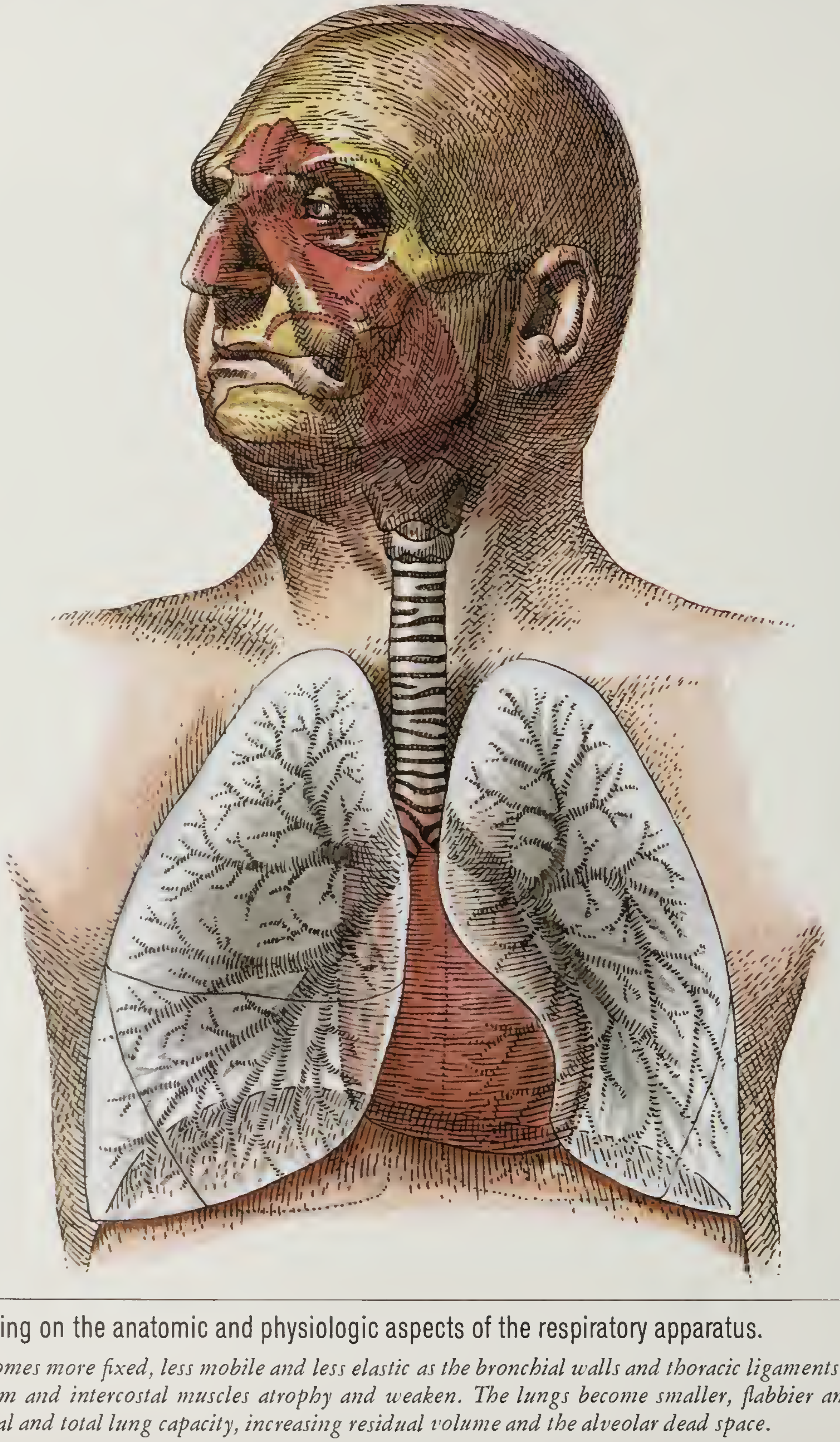
this issue: the common cold and the aging patient

the common cold and the aging patient

Louis J. Vorhaus, II, M.D., F.A.C.P.



G. SCHWENK

Effects of aging on the anatomic and physiologic aspects of the respiratory apparatus.

The chest becomes more fixed, less mobile and less elastic as the bronchial walls and thoracic ligaments lose elasticity. The diaphragm and intercostal muscles atrophy and weaken. The lungs become smaller, flabbier and weigh less, decreasing vital and total lung capacity, increasing residual volume and the alveolar dead space.

Sir William Osler described pneumonia as the welcome friend of the aged patient, because the patient with pneumonia usually died quietly. But today, the well-informed physician is an even better friend of the aging patient, since it is better to live than to die, no matter how quietly.

One of the first avenues of approach in the control of the hazards of respiratory disease in the aging patient is prompt and proper attention to the common cold or upper respiratory infection. The common cold may be the first step in the relatively short path to lower respiratory infection, broncho-pneumonia and death. This train of events occurs frequently among older persons. Indeed, pneumonia is one of the most common causes of their admission to hospitals and ranks high on the list of geriatric killers. Colds are more debilitating in elderly people and the aged are more likely candidates for secondary infections such as sinusitis and bronchitis. These infections, in turn, are more prone to lead to bronchopneumonia, because of lowered resistance and anatomic and physiologic changes in the lungs of the elderly.

What is different about the respiratory tree of an aged person and that of an otherwise healthy younger adult? Aging certainly takes its toll on all parts of the body, affecting both anatomic and physiologic aspects of the respiratory apparatus. These changes are in part due to the wear and tear that occurs over the years; the repeated bouts of respiratory infection, long exposure to atmospheric pollutants, to occupational inhalants, smoking, malnutrition, obesity, inactivity and the development of other diseases which may affect the lungs.

With the passage of years, the lungs change. They become scarred and emphysematous and lose their compliance. The whole chest becomes more fixed, less mobile and less elastic.

The anatomic changes that occur in aging render the lungs less efficient. Tests of pulmonary function in senescence show a deterioration characterized by a decrease in vital capacity and total lung capacity, an increase in residual volume and alveolar dead space. Maximum breathing capacity is reduced and uniformity of ventilation deteriorates. These problems are often aggravated by the obstructed breathing, fever and secondary infection associated with the common cold, placing an additional stress on the entire cardiopulmonary reserve.

In addition, the efficiency of a cough is below par in older persons even though they are in good health. This is partly due to the decreased respiratory excursions and distensibility of the chest wall, and partly from loss of elasticity of bronchial walls which tend to make them collapse in a cough.

The elderly patient's resistance to infection is often reduced. Nutritional deficiencies are more common in aged people. There is some evidence to indicate that their capacity to respond to stress is less efficient. Finally, there is often relatively meager symptomatic response to acute disease. The absence of obvious or dramatic clinical signs and symptoms of severe illness is particularly dangerous because, coming as it

(concluded on following page)

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does in a person whose defenses are weakened both locally and systemically, pulmonary disease may progress rapidly to irreversible stages before medical attention is sought. Respiratory infection is especially hazardous because the aged patient responds badly to hypoxia. Not only is his response to oxygen lack impaired, but the work of breathing, due to decreased compliance of the lung and increased stiffness of the thorax, is markedly augmented.

Many patients late in life are in a precarious and delicate cardiopulmonary balance which is easily decompensated from relatively minor insults such as colds and upper respiratory infections.

For all of these reasons, geriatricians long have stressed the importance of preventing respiratory insults. Today we have better ways of treating respiratory infection, improved techniques for clearing the lungs and bronchial tubes of secretions and better understanding of ways of improving ventilation. We possess a broader spectrum of antimicrobial agents including newer ones to deal with previously resistant organisms. Even so, the death rate from pneumonia is high in older people, and it is preferable to avoid the disease than to treat it. To do so, attention must be paid to the general maintenance of good health and all that implies, as well as to the prevention, elimination and treatment of associated conditions that predispose to or cause pneumonia such as chronic upper or lower respiratory infection, respiratory allergy, chronic sinusitis and exposure to inspired irritants.

Colds and other minor respiratory infections, which favor the development of broncho-pneumonia, should be treated vigorously and promptly, particularly those patients whose aging process has been accompanied by the development of chronic pulmonary disease. Upper respiratory passages should be cleared with decongestants. Sinuses should be drained adequately. And, when indicated, appropriate antimicrobial therapy should be instituted before serious infection of the lower respiratory tree supervenes.

In decades past it was understandable that physicians welcomed pneumonia for the aged patients because it offered them a quiet and peaceful demise. Today we recognize that in many cases, peaceful as it may have been, such deaths were often avoidable. With the current knowledge and understanding of the problems that respiratory infections impose on aging people, vigilant medical attention can often restore them to a vigorous, rewarding and productive life so that the many opportunities that exist today for people to enjoy their golden years are realized and not stolen by untimely death.

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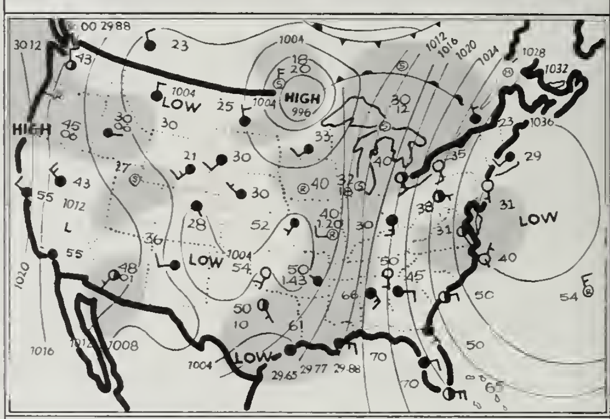
Weather Forecast Throughout the Nation



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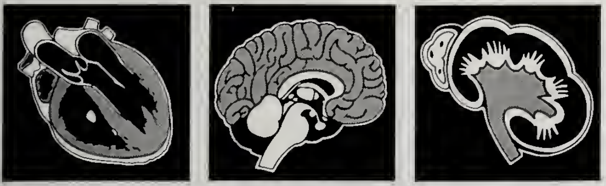
SQUIBB NOTES ON THERAPY

Behind continued high blood pressure readings lies the possibility of organic damage[1-13]

MANY OF THE aspects of essential hypertension are unpredictable—either because there are a number of mechanisms involved or because individuals differ in their responses to these mechanisms.[1]

There is one aspect of hypertension, however, that seems, in many cases, predictable. ". . . when the blood pressure is elevated to a marked degree for an adequate period of time, this in itself leads to perpetuation of the syndrome with resulting vascular damage throughout the body."[14] All too often the disease progresses until there is damage to one of three vital organs: the heart, the kidney, the brain.



"Hypertension is certainly a major factor in the genesis of coronary heart disease, and it is even more important when compounded with obesity."[4]

"[Vascular deterioration] can be clearly seen in the kidney with a degree of damage that can be measured by renal function studies."[10]

". . . most evidence suggests that reduction of blood pressure, when it is too high, not only relieves the heart of excess work but reduces vascular damage."[1]

"In short, treatment is indicated."[1]

Antihypertensive therapy will not restore the blood vessels to normal. Yet many of the vascular changes and symptoms caused by increased blood pressure may be arrested or alleviated when the blood pressure is reduced to normotensive levels.[7]

Reducing the blood pressure helps curtail further vascular damage and improves the prognosis — when damage is not too far advanced before therapy is started.[14] Essential hypertension is an indication not only for treatment, but for *early* and adequate treatment of the patient in question.

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Rautrax-N combines the antihypertensive-tranquilizing action of whole root rauwolfia with the antihypertensive-diuretic action of bendroflumethiazide in one convenient medication. The two drugs complement each other so that smaller doses of both are possible.

Rauwolfia combined with bendroflumethiazide is particularly effective in long-term therapy,[15-17] since beneficial effects do not diminish with continuous daily administration.

For most patients 1 or 2 Rautrax-N tablets daily are sufficient for maintenance therapy. The simplicity, convenience and economy of such a dosage schedule are of particular benefit to older patients.

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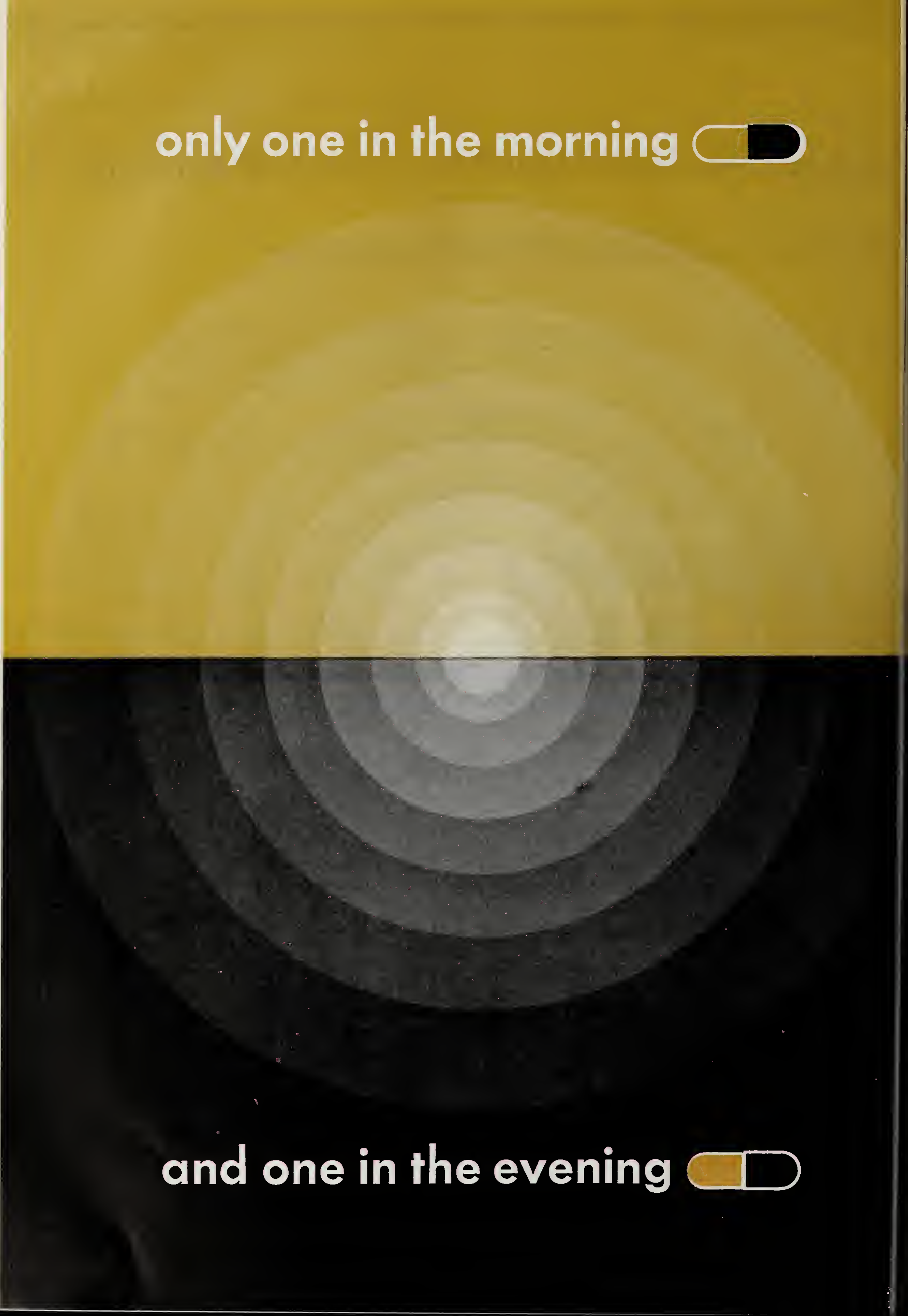
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More of the active antibiotic in the blood. The basic tetracycline in Tetrex (tetracycline phosphate complex) is less bound to serum protein than is demethylchlortetracycline.[1] Result: Tetrex (tetracycline phosphate complex) provides a higher percentage of active antibiotic in the blood.

Available in bottles of 16 and 50.

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BRISTOL LABORATORIES
Division of Bristol-Myers Company
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BRISTOL THERAPEUTIC SUMMARY: For complete information consult Official Package Circular. *Indications:* Infections of respiratory, gastrointestinal and genitourinary tracts and skin and soft tissues due to tetracycline-sensitive organisms. *Contraindications:* The drug is contraindicated in individuals hypersensitive to tetracycline. *Warnings:* Photodynamic reactions have been produced by tetracyclines. Natural and artificial sunlight should be avoided during therapy. Stop treatment if skin discomfort occurs. With renal impairment, systemic accumulation and hepatotoxicity may occur. In this situation, lower doses should be used. Tooth staining and enamel hypoplasia may be induced during tooth development (last trimester of pregnancy, neonatal period and childhood). *Precautions:* Mycotic or bacterial superinfection may occur. Infants may develop increased intracranial pressure with bulging fontanels. In gonorrheal therapy, serologic tests for syphilis should be conducted initially and monthly for 3 months. *Adverse Reactions:* Glossitis, stomatitis, nausea, diarrhea, flatulence, proctitis, vaginitis, dermatitis and allergic reactions may occur. *Usual Adult Dose:* 500 mg. b.i.d. Continue therapy for 10 days in beta-hemolytic streptococcal infections. Administer one hour before or two hours after meals.

Reference: 1. Roberts, C. E., Jr.; Perry, D. M.; Kuhoric, H. A., and Kirby, W. M. M.: A. M. A. Arch. Int. Med. 107:204 (Feb.) 1961.

Each bidCAP contains: Tetrex (tetracycline phosphate complex equivalent to 500 mg. tetracycline HCl activity).

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of snips and snails and puppy dog tails...and a big curiosity that can lead to danger

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TROUBLE!

This could be the beginning of a tragedy It is estimated that over one million people—half of them children under 4 years old—will swallow some kind of poison this year You can protect your family from accidents like this by "Poison proofing" your home today Make sure that all medicines and household products are kept out of the reach of children preferably in a locked cabinet Clean out your medicine cabinet regularly, and dispose of old prescriptions after they've served their purpose And be sure that all medication is clearly labeled and that you *read* the label before taking any medicine or giving it to your children Always remember that youngsters love to imitate grown-ups, so never take medicine in their presence They just might try to take it themselves when you're not around This is Poison Prevention Week Do your part in helping to prevent accidental poisonings The pharmacist at your nearby Peoples Drug Store urges you to come in and get a free Counter-dose Chart today It could save the life of someone very dear to you Let's make every week Poison Prevention Week!

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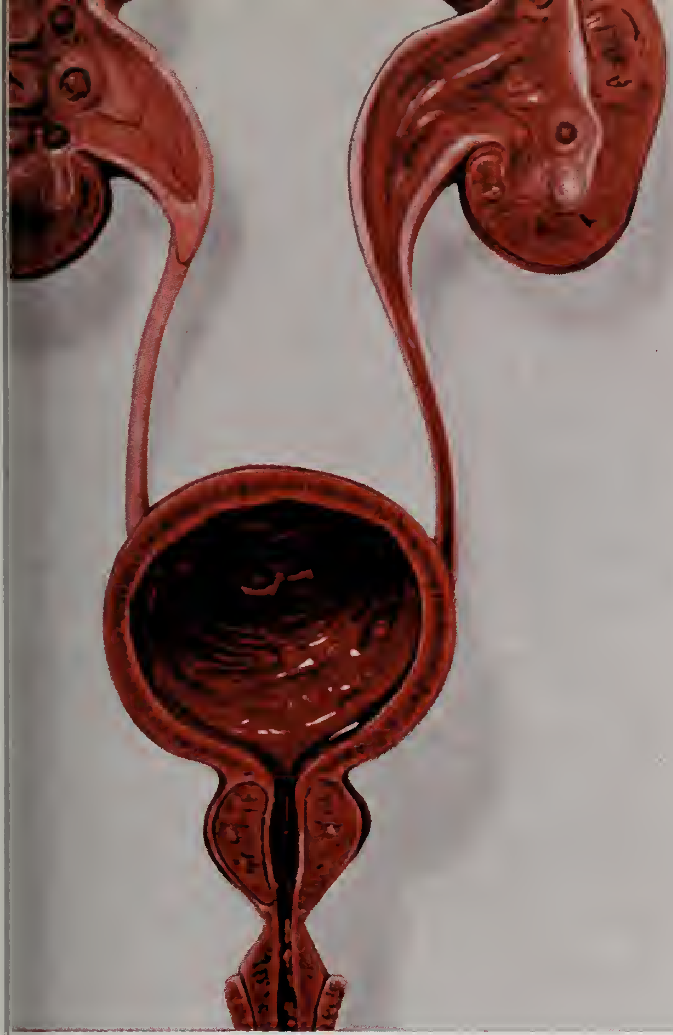

Diagnosis:

cystitis?
pyelonephritis?
pyelitis?
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prostatitis?

in any case,
usually gram-negative*

Therapy:

two 500 mg. Caplets® q.i.d.
(initial adult dose)

NegGram®

Brand of
nalidixic acid

a specific anti-gram-negative

eradicates most urinary tract infections...

- Low incidence of untoward effects; no fungal overgrowth, crystalluria, ototoxic or nephrotoxic effects have been observed.
- "Excellent" or "good" response reported *in more than 2 out of 3* patients with either chronic or acute gram-negative infections.[1]

*As many as 9 out of 10 urinary tract infections are now caused by gram-negative organisms: E. coli, Klebsiella, Aerobacter, Proteus, Paracolon or Pseudomonas[2]... However, infections of the urethra and prostate caused by non-gonococcal gram-negative organisms are believed to be less prevalent.

dications: Urinary tract infections caused by gram-negative and some gram-sitive organisms.

de effects: Mainly mild, transient gastrointestinal disturbances; in casional instances, drowsiness, fatigue, pruritus, rash, urticaria, mild sinophilia, reversible subjective visual disturbances (overbrightness of hts, change in visual color perception, difficulty in focusing, decrease in ual acuity and double vision), and reversible photosensitivity reactions. rked overdosage, coupled with certain predisposing factors, has produced ief convulsions in a few patients.

ecautions: As with all new drugs, blood and liver function tests are advis-le during prolonged treatment. **Pending further experience, like most emotherapeutic agents, this drug should not be given in the first trimester pregnancy. It must be used cautiously in patients with liver disease or vere impairment of kidney function.** Because photosensitivity reactions have curred in a small number of cases, patients should be cautioned to avoid necessary exposure to direct sunlight while receiving NegGram, and if a action occurs, therapy should be discontinued. The dosage recommended adults and children should not arbitrarily be doubled unless under the reful supervision of a physician. Bacterial resistance may develop.

en testing the urine for glucose in patients receiving NegGram, Clinistix® agent Strips or Tes-Tape® should be used since other reagents give a se-positive reaction.

sage: Adults: Four Gm. daily by mouth (2 Caplets® of 500 mg. four times ily) for one to two weeks. Thereafter, if prolonged treatment is indicated, dosage may be reduced to two Gm. daily. Children may be given proximately *25 mg. per pound* of body weight per day, administered in ided doses. The dosage recommended above for adults and children ould not arbitrarily be doubled unless under the careful supervision of a ysician. Until further experience is gained, infants under 1 month ould not be treated with the drug.

w supplied: Buff-colored, scored Caplets® of **500 mg. for adults,** conve-ently available in bottles of 56 (sufficient for one full week of therapy) and in ttles of 1000. **250 mg. for children,** available in bottles of 56 and 1000.

ferences: (1) Based on 23 clinical papers, 1512 cases. Bibliography on quest. (2) Bush, I. M., Orkin, L. A., and Winter, J. W., in Sylvester, J. C.: timicrobial Agents and Chemotherapy – 1964, Ann Arbor, American ciety for Microbiology, 1965, p. 722.

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Vistaril
(HYDROXYZINE)

tranquilizes without addiction or drug dependency

Clinical Experience

In its eight-year record of experience in which over one billion doses have been prescribed, there is no evidence of addiction to hydroxyzine.

Clinical Background

In over 500 published studies involving 15,000 individual cases, neither dependency nor addiction has been reported with hydroxyzine.

Since 1849
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Science for the world's well-being®

Even in the anxious, dependent, psychoneurotic...

Four hundred and fifty patients, most of them classified as functional neurotics, were treated with hydroxyzine for periods of five months to four and one-half years. Sustained good-to-excellent relief from symptoms of anxiety and tension was attained in 401 (89%) of the series. "*Cumulative effects, habituation or addiction to hydroxyzine was not noted during the entire period of this study.*"

halowitz, M.: Int. Rec. Med. 174:357, June, 1961.

ven in the classically dependent alcoholic...

istaril (hydroxyzine) was evaluated for relief f postalcoholic syndrome in 52 chronic alcoholic utpatients over a period of two to four weeks. lany patients received partial to complete relief f psychomotor agitation, anxiety, irritability, raving, insomnia, depression, anorexia, nausea and ension. "*No evidence of toxicity or habituation as noted.*" "*No difficulty was experienced n discontinuing medication.*"

reenhouse, H. R.: Med. Times 91:1069, November, 1963.

f 326 alcoholics treated with hydroxyzine for the ostalcoholic syndrome, satisfactory control was chieved in 276 (85%). "*As is not the case with other anquilizers, hydroxyzine has no published record of ausing addiction and dependence or withdrawal ymptoms.*" Goldman, H. I.: Southwest. Med. 42:276, June, 1961.

ven in the nstitutionalized patient eeding long-term reatment...

ne hundred and fifty-two institutionalized male patients were studied on long-term, igh-dose therapy.
ven at high dosages, hydroxyzine
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polla, A.: Clin. Med. 8:1332, July, 1961.

No other tranquilizer is as precise, as uncomplicated as Vistaril®

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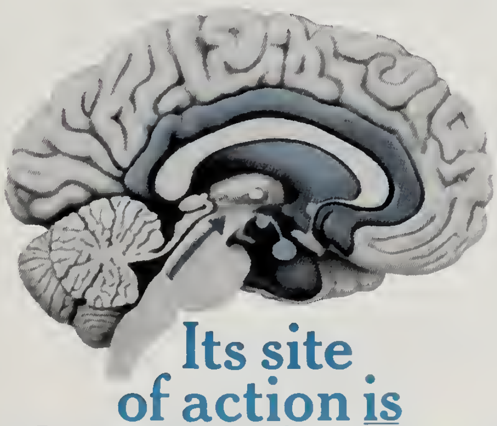

Its site of action is the seat of anxiety

turn page for brief summary . . .

BRIEF SUMMARY

Contraindications: Hypersensitivity to hydroxyzine. The parenteral solution, for intramuscular or intravenous use, ***must not*** be injected subcutaneously or intra-arterially.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available, to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants. In conjunctive use, dosage for these drugs should be decreased, as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. On reported intravenous injection a few instances of digital gangrene have occurred distal to the injection site, considered to be due to inadvertent intra-arterial injection or possibly periarterial extravasation. Therefore, particular caution should be observed to insure injection only into intact veins; avoid either intra-arterial injection or extravasation. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity has been reported in some hospitalized patients given higher than recommended dosage.

When this product is given intravenously undiluted, minimal amounts of intravascular hemolysis occur at the site of injection. Giving the maximum recommended intravenous dose (100 mg.) to adults results in immediate transient hemolysis with the liberation of a total of 2-3 grams of hemoglobin, which, in some individuals, can cause small amounts of hemoglobinuria. This compares with the normal red cell destruction from which approximately 8 Gm. of hemoglobin are liberated every 24 hours. If the hydroxyzine is diluted with 50 cc. of normal saline and given during a period of four minutes or more, this phenomenon does not occur.

Supply: Vistaril (hydroxyzine pamoate) Capsules: Equivalent to 25 mg., 50 mg., 100 mg. hydroxyzine HCl. Vistaril (hydroxyzine pamoate) Oral Suspension: Equivalent to 25 mg. hydroxyzine HCl per 5 cc. teaspoonful. Vistaril (hydroxyzine HCl) Parenteral Solution: 25 mg./cc.—10 cc. vial and 50 mg./cc.—2 cc. and 10 cc. vial; Isoject,® 25 and 50 mg. per cc., 1 cc. per unit.

More detailed professional information available on request.

The Vistaril site of action is the seat of anxiety

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Over the Desk

Ear Bones Pledged to Science: Dr. Gordon Hoople, Medical Adviser to The Deafness Research Foundation, paid tribute to an unusual action by leaders of a national organization of the deaf as "the most significant and unique contribution ever made by the deaf to the cause of otologic research."

The contribution was the bequeathing of their inner ear structures to ear research scientists by every member of the Board of Directors, and their wives, of the National Association of the Deaf.

"The ears of the profoundly deaf," said Dr. Hoople, "have been virtually impossible to obtain for scientific studies in the past. Because of the very affliction from which they suffer—deafness—they cannot be reached through normal communication, yet it is essential to have their bequeathed inner ear structures before many of the causes of nerve deafness can be found. The fact is that the inner ear, where much deafness originates, is inaccessible and therefore cannot be seen or examined during one's lifetime."

The Temporal Bone Banks Program for Ear Research has created a network of 41 ear research laboratories coördinated in activity by 4 Regional Centers, where the pledged inner ear structures are processed and studied in conjunction with the donor's lifetime medical records.

The program is conducted by The Deafness Research Foundation in Coöperation with the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology.

Further information and pledge forms may be obtained by writing to The Deafness Research Foundation, 366 Madison Avenue, New York, N. Y. 10017.—The Deafness Research Foundation News, June 6, 1966.

⁂

Operation Emergency Airlift: When the airlines strike hit, July 9, Squibb, the pharmaceutical manufacturer, refused to be grounded. Instead, Squibb chartered 3 planes and launched Operation Emergency Airlift to bring its critically-needed radioactive compounds to the Nation's medical centers.

Between July 9 and July 27 more than 4,000 deliveries of Squibb radiopharmaceuticals have

(*Continued on page 30*)

SQUIBB NOTES ON THERAPY

Breast-feeding and the "modern mother"

Despite a mild resurgence of interest in the importance of breast-feeding a few years ago, many women today do not choose to nurse their young. This is for a variety of reasons—social, economic, cultural and sometimes medical. In such cases the physician's task is to find the most suitable means of preventing lactation and easing the pain of breast engorgement.

The means of therapy

The value of hormone therapy for this indication is of course well established. Both androgen and estrogen are known to inhibit the production and secretion of the lactogenic hormone by the anterior pituitary. As estrogen levels decline sharply at parturition, lactogenesis is established. When androgen and estrogen are administered to the patient before the release of the lactogenic hormone lactation and breast engorgement are usually prevented.

The time of therapy

The time of administration of this combined medication is crucial; it must be given early enough to suppress the pituitary prolactin and last long enough to permit physiologic readjustment during the puerperium. Excellent results are most often seen when therapy is administered before the onset of the second stage of labor.

However, factors other than effectiveness must also be considered. The agent selected should not interfere in any way with parturition, subsequent uterine involution and the restoration of normal ovarian cyclic function. Furthermore, it should not cause rebound breast engorgement or other manifestations of hormonal imbalance.

A balanced formulation

Providing single-dose therapy for the prevention of lactation and breast engorgement, Deladumone OB is a potent androgen-estrogen combination with a prolonged action. The optimal balance of androgenic and estrogenic hormones achieved in this preparation minimizes the disadvantages inherent in single hormone therapy, such as rebound breast engorgement. Involution of the uterus and resumption of menstrual cycles are not affected.

As reported in a recent published study (Roser, D. M.: Obstet. & Gynec. *27*:73, 1966), Deladumone OB provided good suppression of breast engorgement in 95.3% and suppression of lactation in 81.1% of 86 obstetrical patients. These results are in general agreement with those of many earlier investigations; in several studies this injectable androgen-estrogen combination proved to be superior to oral medication.

Dosage:

As a single injection of 2 cc. before the onset of the second stage of labor.

Contraindications:

Established or suspected mammary cancer or genital malignancy.

Precautions and Side Effects:

Certain patients may be unusually responsive to either estrogenic or androgenic therapy. In such individuals virilization, uterine bleeding or mastodynia may occur.

Supply:

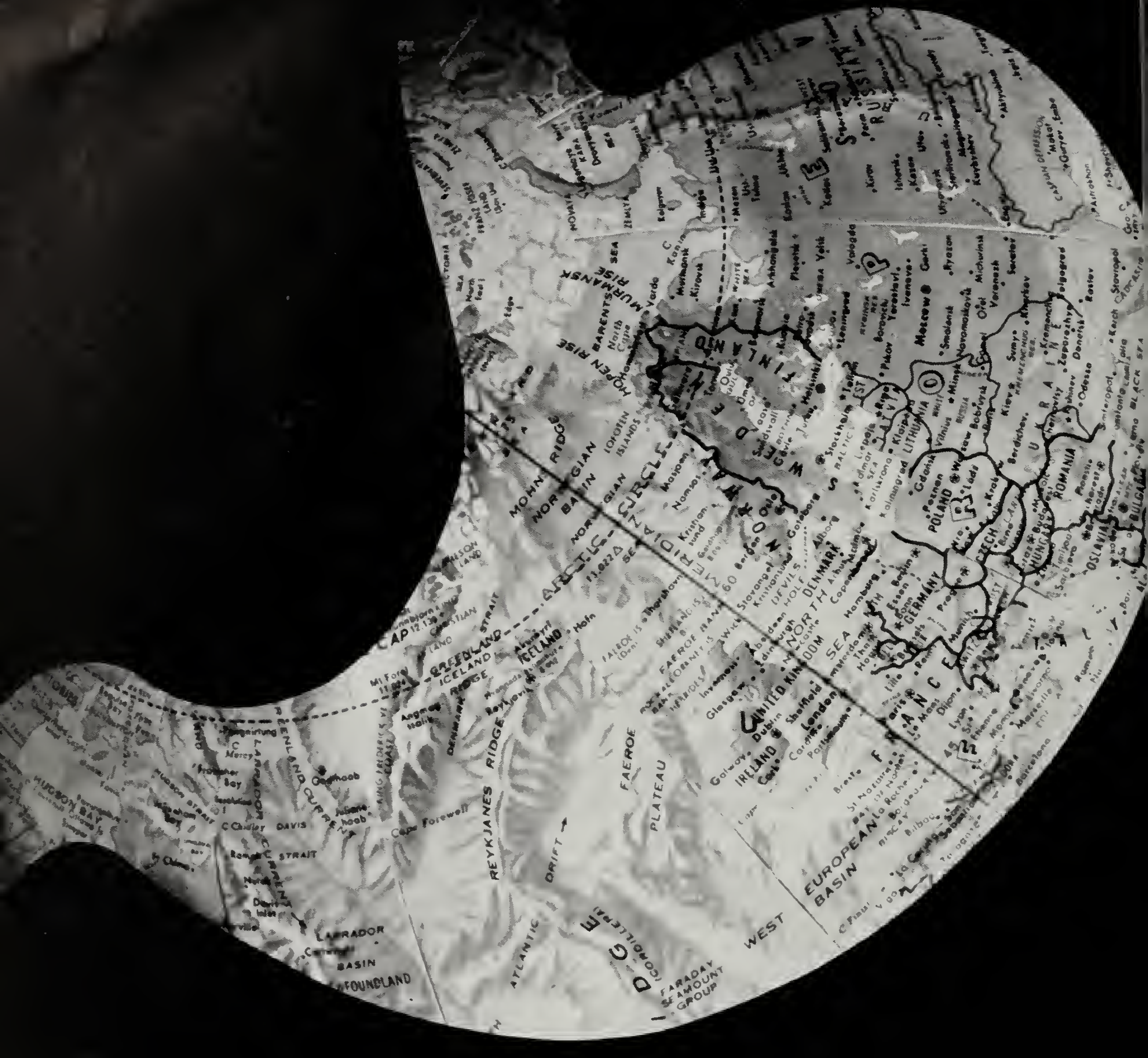
Deladumone OB, providing 180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc., is available in 2 cc. Unimatic® disposable syringes and in 2 cc. vials. Both preparations are dissolved in sesame oil, with 2% benzyl alcohol as a preservative. *Before use, consult product literature for full prescribing information.*

Deladumone® OB

Squibb Testosterone Enanthate (180 mg./cc.) and Estradiol Valerate (8 mg./cc.)

Single-dose injection for lactation inhibition

SQUIBB *'The Priceless Ingredient' of every product is the honor and integrity of its maker.*



The "Socio-geographic" mystery

Why is one man's gastric ulcer another man's duodenal?

Geographic variation in the *incidence* of peptic ulcer is a familiar fact. But the proclivity of certain *kinds* of ulcer for certain geographic areas is a recently recognized phenomenon.[1,2]

For example, in one particular Norwegian fishing village there is a tendency for patients to develop a gastric ulcer; anywhere else in Norway, ulcers are usually duodenal. Peruvians high in the Andes have more gastric ulcers than their compatriots in the lowlands. Why? Nobody knows.

Social variations, too. Even in the same geographic areas there are interesting variations. An Englishman's ulcer depends on his social standing—professional men suffer with duodenal ulcers, while workingmen have more of the gastric variety. In southern India the pattern is reversed. Here, duodenal ulcers are common among laborers and agricultural workers and rare among the upper classes.

Investigators are exploring every possible theoretical avenue in their search for the cause of peptic ulcer. Of all the factors implicated in ulcerogenesis, the one that is generally acknowledged to be of primary importance is hypersecretion of gastric acid.[3-8] Or, as one author states it: "The medical management of peptic ulcer pharmacologically is, in the final analysis, concerned largely with the effective inhibition of peptic activity."[3]

Robinul (glycopyrrolate) provides potent, rapid, specific antisecretory action confirmed by gastric analyses and x-ray evidence of clinical effectiveness.[3,7,9-12] Relieves pain with "impressive" promptness.[8] Quickly alleviates acute discomfort, and effectively counteracts gnawing pain, preprandial midepigastric pain, belching and other ulcer symptoms.[7] Suppression of nocturnal pain is "outstanding."[13] Maximally effective doses may be given with minimal side reactions, and the incidence of unwanted anticholinergic effects is negligible.[3,7-14]

no matter what the ulcer theory...the fact is that

Robinul®
(glycopyrrolate)

promotes the essential ulcer-healing environment

A·H·ROBINS

(brief summary follows)

R10A66

Robinul®
(glycopyrrolate)
promotes the essential ulcer-healing environment

Indications: In addition to its primary indications for duodenal and gastric ulcer, Robinul (glycopyrrolate) is indicated for other GI conditions that may benefit from anticholinergic therapy. Robinul-PH Forte (glycopyrrolate 2 mg. with phenobarbital) is indicated when these situations are complicated by mild anxiety and tension.
Contraindications: Glaucoma, urinary bladder neck obstruction, pyloric obstruction, stenosis with significant gastric retention, prostatic hypertrophy, duodenal obstruction, cardiospasm (megaesophagus), and achalasia of the esophagus, and in the case of Robinul-PH Forte, sensitivity to phenobarbital.
Precautions: Administer with caution in the presence of incipient glaucoma.
Adverse Reactions: Dryness of the mouth, blurred vision, urinary difficulties, and constipation are rarely troublesome and may generally be controlled by reduction of dosage. Other side effects associated with the use of anticholinergic drugs include tachycardia, palpitation, dilatation of the pupil, increased ocular tension, weakness, nausea, vomiting, headache, dizziness, drowsiness, and rash.
Dosage: Dosage should be adjusted according to individual patient response. Average and maximum recommended dose is 1 tablet 3 times a day: in the a.m., early p.m., and at bedtime. *See product literature for full prescribing information.*
Supply: Robinul (glycopyrrolate 1 mg.); Robinul Forte (glycopyrrolate 2 mg.); Robinul-PH (glycopyrrolate 1 mg.) with phenobarbital 16.2 mg. (Warning: May be habit-forming); Robinul-PH Forte (glycopyrrolate 2 mg.) with phenobarbital 16.2 mg. (Warning: May be habit-forming.) In bottles of 100 and 500 scored tablets.
References: 1. Jones, F. A., and Gummer, J. W. P.: Clinical gastroenterology, Springfield, Ill., Charles C Thomas, 1960, pp. 322-3. **2.** Bockus, H. L.: Gastroenterology, 2nd ed., vol. 1, Philadelphia, Saunders, 1963, p. 468. **3.** Sun, D. C. H.: Ann NY Acad Sci 99:153 (Feb. 28) 1962. **4.** Moore, V. A.: Postgrad Med 38:216 (Sept.) 1965. **5.** Dragstedt, L. R., Woodward, E. R., Storer, E. H., Oberhelman, H. A., Jr., and Smith, C. A.: Ann Surg 132:626 (Oct.) 1950. **6.** Posey, E. L., Jr., Smith, P., Turner, C., and Aldridge, J.: Amer J Dig Dis 10:399 (May) 1965. **7.** Lamphier, T. A., Siegel, L., and Goldberg, R. I.: Amer J Gastroent 37:551 (May) 1962. **8.** Kasich, A. M., and Fein, H. D.: Ibid 39:61 (Jan.) 1963. **9.** Epstein, J. H.: Ibid 37:295 (Mar.) 1962. **10.** Moeller, H. C.: Ann NY Acad Sci 99:158 (Feb. 28) 1962. **11.** Slanger, A.: J New Drugs 2:215 (Jul.-Aug.) 1962. **12.** Barman, M. L., and Larson, R. K.: Amer J Med Sci 246:325 (Sept.) 1963. **13.** Shutkin, M. W.: Amer J Gastroent 38:682 (Dec.) 1962. **14.** Fleshler, B.: J New Drugs 2:211 (Jul.-Aug.) 1962.

A. H. ROBINS CO., INC.
Richmond, Virginia

Over the Desk

(*Continued from page 26*)

been made to more than 100 United States medical teaching centers, Veterans Administration and military hospitals, and the Clinical Center of the National Institutes of Health, Bethesda, Md.

Cost to Squibb of the airlift is more than $25,000 per week.—News Release, July 28, 1966, from E. R. Squibb & Sons, Inc.

* * *

Drop in New Pharmaceutical Products: National introductions of new medicines by American drug companies declined sharply during the first 6 months of 1966 to the lowest point in 25 years.

Summary of New Products
First Six Months of Each Year

	1966	1965	1964	1963	1962	1961
Single chemical entities	4	14	8	8	14	24
Duplicate products	5	8	19	16	29	22
Combination products	30	33	71	65	82	108
TOTAL	39	55	98	89	125	154

New drug products consist of single chemical entities, duplicates of existing products, and new combinations of existing products.

The approved single new chemicals are: a local anesthetic, an antileukemic, a topical antibiotic, and an ingredient in an anovulatory product.—Paul de Haen, Inc. Drug Information Services, July 28, 1966.

* * *

Pharmaceutical Philantropist Honored: Eli Lilly, an Indianapolis philanthropist who has been associated for more than half a century in the manufacture of prescription medicines, was honored, March 7, for distinguished service to the deaf. The Alexander Graham Bell Association for the Deaf presented the 1966 Alexander Graham Bell Award to Lilly. The presentation was made at the City Tavern in Georgetown.

Lilly, a grandson of the founder of the pharmaceutical company which bears his name, is treasurer of the Lilly Endowment, Inc., a family foundation granting bequests annually in several fields of human endeavor.—*The Washington Post*, March 8, 1966.

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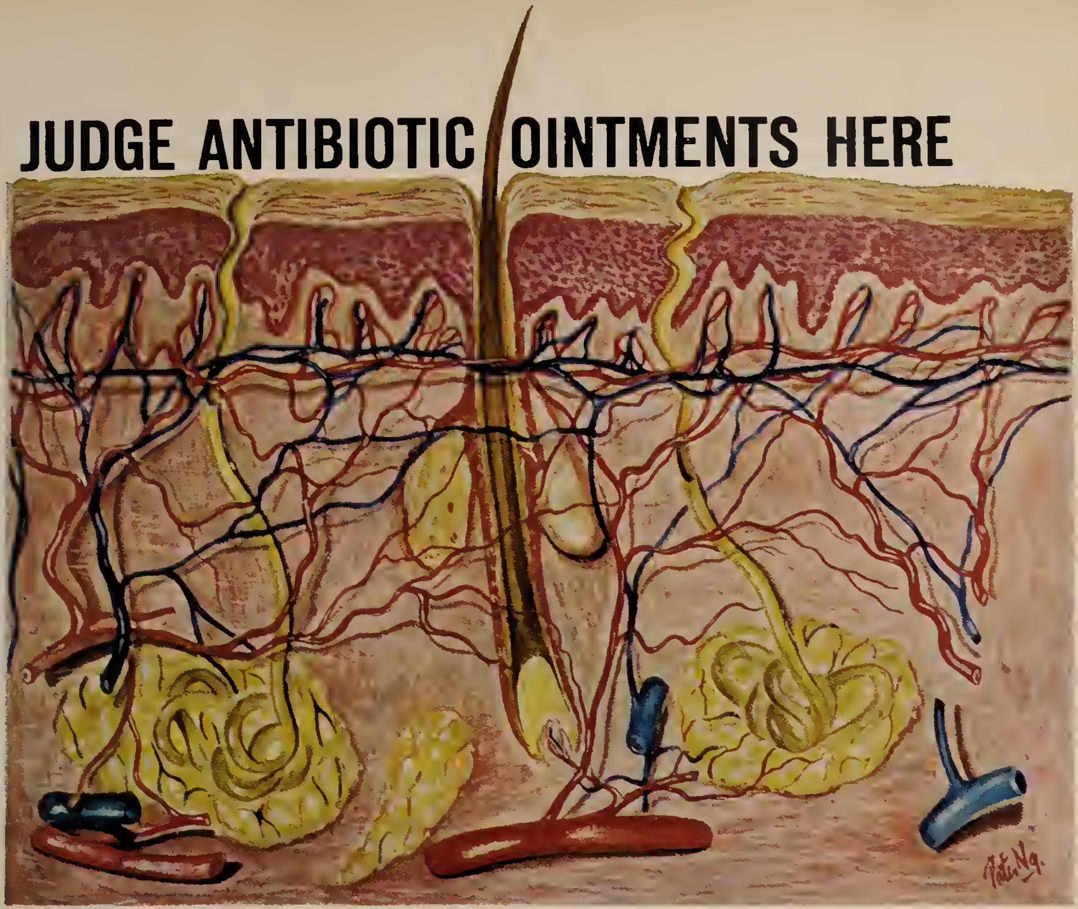

Results on skin are final proof of any topical antibiotic's effectiveness

No in vitro test can duplicate a clinical situation on living skin. 'Neosporin' (polymyxin B—bacitracin—neomycin) Antibiotic Ointment has consistently proven its effectiveness in thousands of cases of bacterial skin infection. The spectra of the three antibiotics overlap in such a way as to provide bactericidal action against most pathogenic bacteria likely to be found topically. Diffusion of the antibiotics from the special petrolatum base is rapid since they are insoluble in the petrolatum, but readily soluble in tissue fluids. The Ointment is bland and rarely sensitizes.

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a new formulation that relieves pain in tension headache and neuralgia

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Indications: For relief of pain and discomfort of simple headache; neuralgia, myalgia, and musculoskeletal pain; dysmenorrhea; bursitis; sinusitis; fibrositis. Also indicated to reduce fever and to relieve discomfort due to respiratory infections, influenza, and other febrile conditions.

Contraindication: Not recommended during pregnancy.

Caution: May be habit-forming. Do not use in patients sensitive to barbiturates or in those with moderate to severe hepatic disease.

Side Effects: Nausea, transitory dizziness, rash. Overdosage of allobarbital produces symptoms typical of acute barbiturate excess.

Dosage: *Adults:* 1 or 2 tablets every 4 hours. Not to exceed 8 tablets in 24 hours. *Children 6 to 12:* ½ to 1 tablet every 4 hours. Not to exceed 4 tablets in 24 hours.

Supplied: *Tablets* (white, scored), each containing 15 mg allobarbital and 300 mg acetaminophen; units of 3 bottles of 30.

For your convenience—prescription-size bottle of 30.

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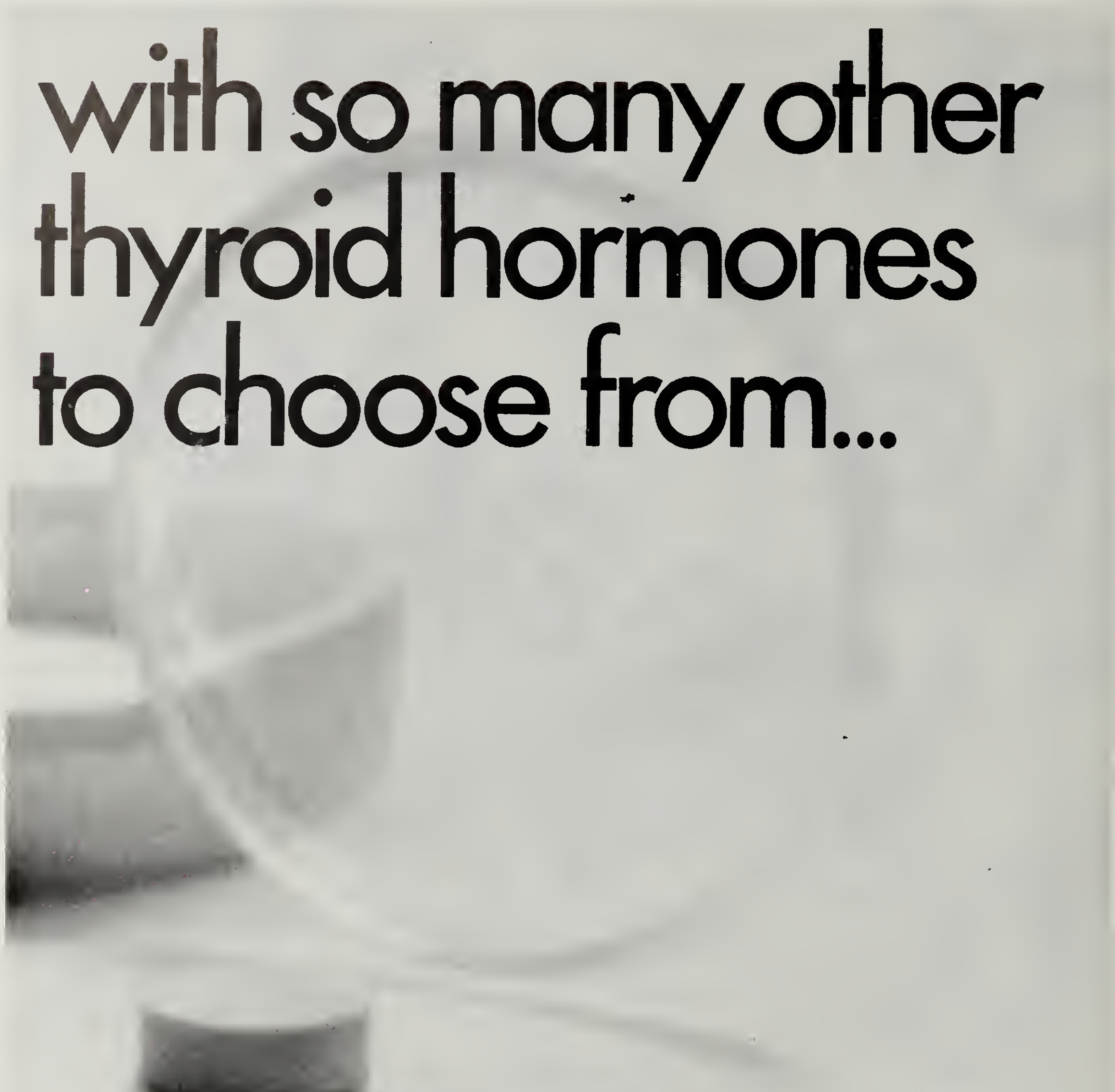
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Expect PBI readings to be in the range of 6-10 mcg. %. Count on these readings and on other parameters to be predictable in relation to the dosage you prescribe. Levothyroxine has a high binding capacity for serum proteins in contrast to other thyroid medicaments which may contain varying amounts of L-triiodothyronine which has a low binding capacity. In patients made euthyroid with SYNTHROID (sodium levothyroxine), it is therefore not unusual to find PBI levels of 8-10 mcg. %.

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Available in six strengths. Tablets are scored and color-coded for dosage convenience. SYNTHROID (sodium levothyroxine) INJECTION is also available.

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SYNTHROID (sodium levothyroxine) duplicates the biological and metabolic activity of endogenous thyroxine. The tablets are specific replacement therapy in diminished or absent thyroid function resulting in hypothyroidism ranging from the subclinical or borderline type to the myxedematous type. The administration of SYNTHROID (sodium levothyroxine) is therefore indicated in primary, hypopituitary, pediatric, and geriatric hypothyroidism, and for reproductive disorders such as infertility, menstrual disturbances and habitual abortion associated with hypothyroidism.

Because SYNTHROID (sodium levothyroxine) is effective in the treatment of hypothyroidism of any degree of severity, it is especially useful in subclinical cases exemplified by symptoms such as undue lassitude, skin disturbances and obesity, in the presence of diagnostic test criteria. In your judgment, when a diminished level of thyroid hormone may be implicated, the purity, stability, and predictability of SYNTHROID (sodium levothyroxine) are particularly important to confirm your diagnosis because they eliminate the variability in response due to product deficiency often encountered with desiccated thyroid.

Precautions: As with other thyroid preparations, an overdose may cause diarrhea or cramps, nervousness, tremors, tachycardia, vomiting and continued weight loss. Medication, in such cases, should be stopped for 2-6 days, then resumed at a lower dose level. In patients with diabetes mellitus, careful observations should be made for changes in parameters that are used to guide antidiabetic therapy. **Contraindications:** Thyrotoxicosis, acute myocardial infarction. **Administration and Dosage:** Administer tablets as a single daily dose, preferably after breakfast. Injection may be administered intravenously in solutions containing 100 mcg. per ml. **Supplied:** Tablets: 0.025 mg., 0.05 mg., 0.1 mg., 0.15 mg., 0.2 mg., 0.3 mg., scored and color-coded, in bottles of 100 and 500. Injection: 500 mcg., lyophilized, in 10 ml. single dose vial, with 5 ml. vial of diluent.

EASY TO PRESCRIBE—EASY TO USE

0.1 mg. SYNTHROID (sodium levothyroxine)
APPROXIMATELY EQUIVALENT TO 1 gr. THYROID U.S.P.

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sodium levothyroxine, FLINT

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Norinyl® **tablets**
(norethindrone 2 mg. c̄ mestranol 0.1 mg.)

for multiple contraceptive action that has produced a record of unexcelled effectiveness

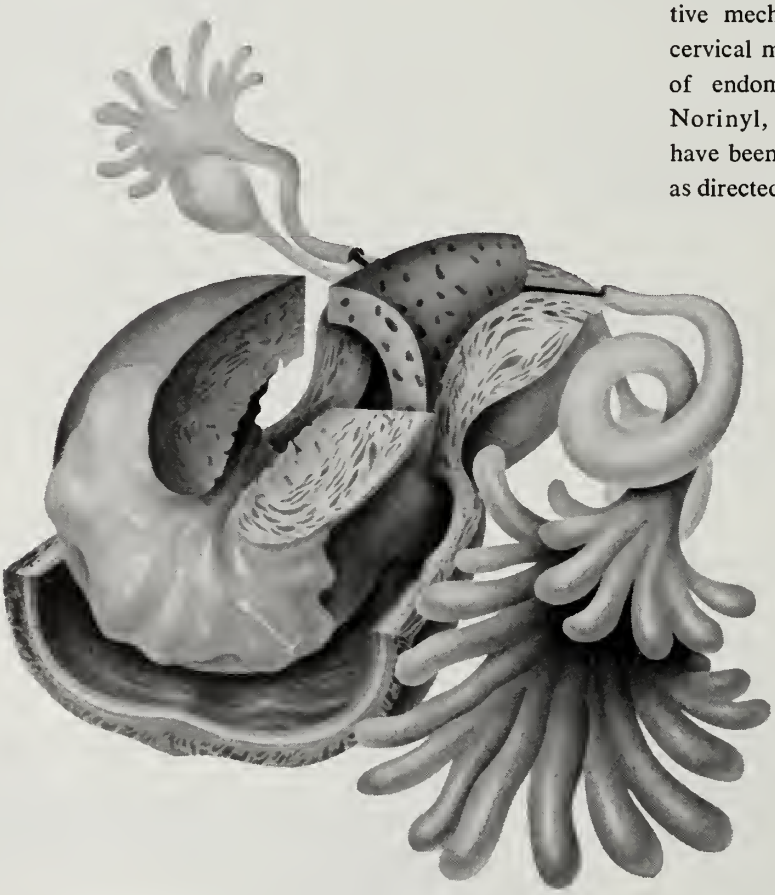
inhibition of ovulation by means of 2 time-proved hormonal agents

production of a cervical mucus hostile to sperm motility and vitality

creation of an endometrium unreceptive to egg implantation

no unplanned pregnancies

Norinyl provides multiple action for maximum assurance of success. It does not depend on ovulation inhibition alone for contraceptive effectiveness. The mechanism of action of combined hormonal therapy results in ovulation inhibition reinforced by other protective mechanisms, including a hostile cervical mucus[1-13] and an acceleration of endometrial changes.[1-3,7-16] With Norinyl, no unplanned pregnancies have been reported to date when used as directed.



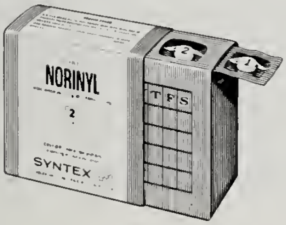
plus important supportive benefits that help her through those critical early months of oral contraception

low incidence of side effects

Low incidence of BTB and spotting, nausea and amenorrhea tends to minimize side effect problems and increases patient cooperation.

no confusion about dosage

An unbreakable "confusionproof" package makes it easy to adhere to prescribed dosage schedule: individually sealed tablets numbered from 1 through 20 *plus* monthly calendar record enables patient to double-check dosage intake by day and corresponding tablet number.



Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: 1. Council on Drugs. JAMA 187 664 (Feb. 29) 1964. 2. Bryans, F. E.: Canad Med Ass J 92:287 (Feb. 6) 1965. 3. Goldzieher, J. W.: Med Clin N Amer 48:529 (Mar.) 1964. 4. Cohen, M. R.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965. 5. Hammond, D. O.: Ibid. 6. Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A.: Fertil Steril 14:402 (Jul.-Aug.) 1963. 7. Goldzieher, J. W., Moses, L. E., and Ellis, L. T.: JAMA 180:359 (May 5) 1962. 8. Kempers, R. D.: GP 29:88 (Jan.) 1964 9. Tyler, E. T.: JAMA 187:562 (Feb. 22) 1964 10. Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M : Fertil Steril 16:158 (Mar.-Apr.) 1965. 11. Flowers, C E., Jr.: N Carolina Med J 25:139 (Apr.) 1964. 12. Goldzieher, J. W : Appl Ther 6:503 (June) 1964. 13. The Control of Fertility. Report adopted by the Committee on Human Reproduction of the American Medical Association. JAMA 194:462 (Oct. 25) 1965. 14. Flowers, C. E., Jr.: JAMA 188:1115 (June 29) 1964. 15. Merritt, R. I.: Appl Ther 6:427 (May) 1964 16. Newland, D. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

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SYNTEX
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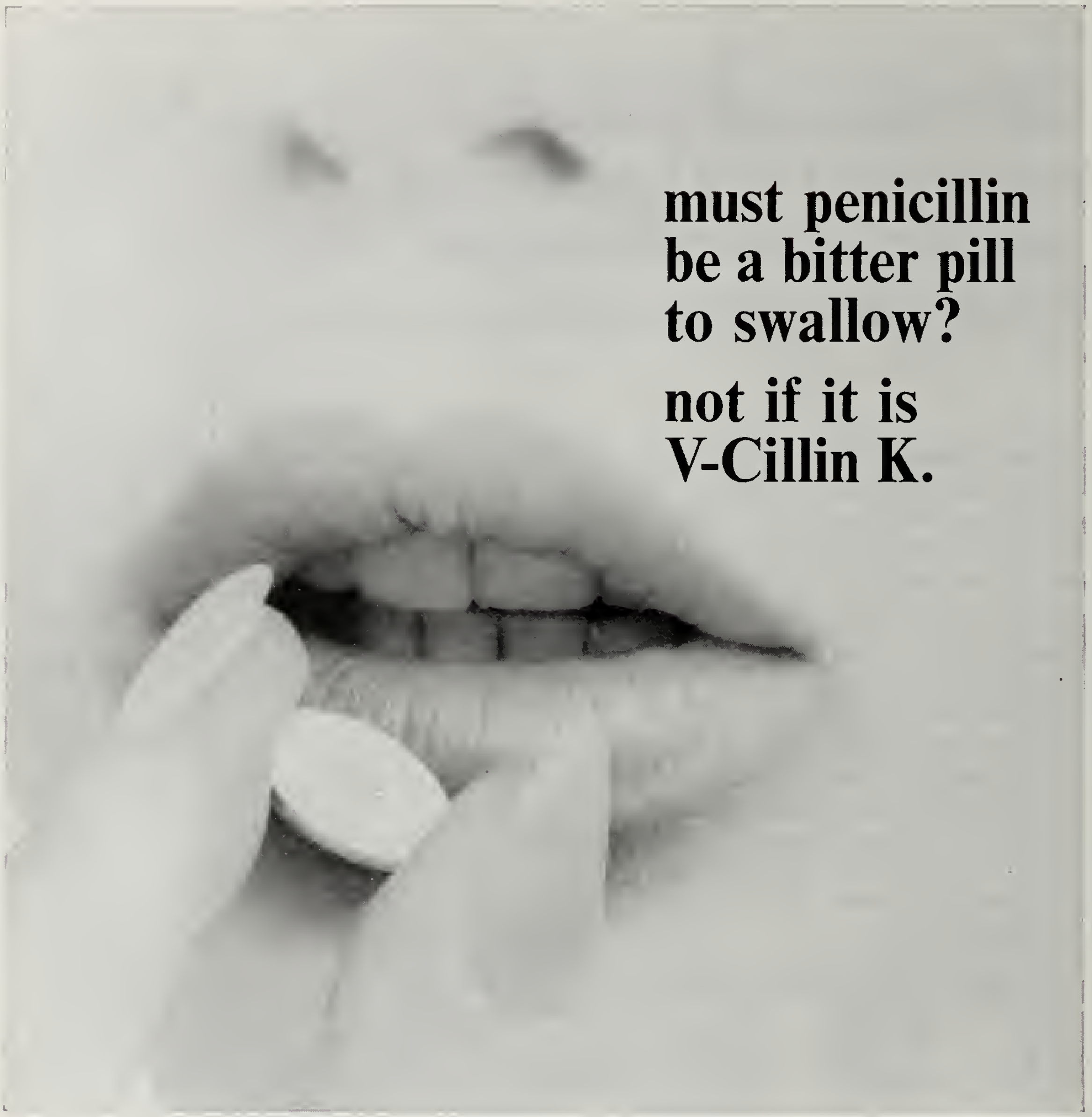
Norinyl® tablets
(norethindrone 2 mg c̄ mestranol 0.1 mg)

for multiple contraceptive action



V-Cillin K now has a unique glossy coating that banishes bitter penicillin taste and makes it easier to swallow. Within six seconds (just long enough for the tablet to get past the taste buds), the coating dissolves and the penicillin is ready for immediate absorption into the bloodstream. The patient still gets all the special benefits of V-Cillin K, including consistent dependability . . . even in the presence of food.

Indications: V-Cillin K is an antibiotic useful in the treatment of streptococcus, pneumococcus, and gonococcus infections and infections caused by sensitive strains of staphylococci.

Contraindications and Precautions: Although sensitivity reactions are much less common after oral than after parenteral administration, V-Cillin K should not be administered to patients with a history of allergy to penicillin. As with any antibiotic, observation for overgrowth of nonsusceptible organisms during treatment is important.

Usual Dosage Range: 125 mg. (200,000 units) three times a day to 250 mg. every four hours.

Supplied: Tablets V-Cillin K, 125 or 250 mg., and V-Cillin K, Pediatric, 125 mg. per 5-cc. teaspoonful, in 40, 80, and 150-cc.-size packages.

V-Cillin K® **Six-Second Barrier to Bitterness**

Potassium Phenoxymethyl Penicillin

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Additional information available to physicians upon request. Eli Lilly and Company, Indianapolis, Indiana 46206.

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MEDICAL ANNALS

of the District of Columbia

October 1966 VOLUME XXXV • NUMBER 10

Cerebral Disturbances from Small Amounts of DDT*

A Controlled Study

ELOISE W. KAILIN, M.D.†, AND ALICIA HASTINGS, M.D.‡

In another study[1] it was found that amounts of the pesticide DDT which are well below those ingested by the average American citizen are capable, in certain selected persons, of reducing electromyographic potentials and causing fatigue, slowed thought, withdrawal from reality, blurred vision, headache and ataxia. This is a matter of considerable concern and, in the emotionally charged climate that envelops the subject of pesticide toxicity in humans, must be tested under circumstances which would eliminate any possible unconscious bias on the part of either the investigator or the subjects being tested. For this reason testing and control samples which could not be distinguished by appearance or odor were given to a physician whose employer is a pesticide regulating agency of the Federal Government. This physician selected test or control samples and observed our administration of these to selected sensitive subjects. Statistical analysis of the results showed good discrimination between test and control specimens. These results could occur on a chance basis in about 1 of 100 trials only. The fact that frequency of identification of DDT samples was related to increasing concentrations of DDT present is further evidence that chance alone did not determine these results.

Subjects and Symptoms

Following avoidance of a variety of additives to food, air and water for at least a week a test substance is presented. If the route of exposure is inhalation and the patient is sensitive to this substance a reaction will start in from 20 seconds to 5 minutes, as a rule. One or more of the following complaints may appear: dimming of vision, drawing sensation at the base of the nose or behind the eyes, sense of fullness deep inside the skull, pulling sensation in head and neck muscles, headache, slowing of thought, and inability to recall events and words or to concentrate on a topic. Emotional responses first take the form of a sense of withdrawal from interpersonal relationships with cessation of conversation. The disinclination to talk or move may be sufficiently intense to resemble catatonia. Secondarily, anxiety and occasionally active hostility may appear. Perception may be altered as to size of objects: "The door looks so much bigger—everything around me is getting bigger!" and vertical or lateral displacements: "The venetian blinds are wavy now." Dimming of vision is described as like trying to look through a filmy grey veil. Somatic effects are also noted. Nasal passages may become stuffy or drippy, and hoarseness, dysphagia, flushing of the face, general relaxation of voluntary muscles with loss of facial expressiveness, and postural relaxation are noted. Uncertain gait and loss of balance are seen, especially with higher dosages or prolonged exposure. One subject regularly develops edema of the eyelids and a linear subcutaneous thickening near the crown of the scalp about 45 to 60 minutes after DDT exposure. Another woman develops sterile abscesses 6 to 10 hours later. Two other patients develop pain and stiffness in the finger joints 1 day after pesticide exposure. Fatigue and malaise may last for days and are often more intense the day following an exposure. Occasionally delayed reaction of this nature occurs without immediate reaction when exposure has been not intense but prolonged. Delayed effects also tend to occur in a subject who has been feeling unusually well for some weeks.

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* This work was aided by U. S. Public Health Service Grant No. GM 11886-02 and the Division of Physical Medicine, Howard University College of Medicine.

† Clinical Assistant Professor of Medicine, Howard University College of Medicine. Reprints: 836 Bonifant Street, Silver Spring, Md. 20910.

‡ Assistant Professor, Division of Physical Medicine, Howard University College of Medicine.

The chemical incitants of reaction are most likely to be either fat solvents or fat-soluble substances. Chemical configuration patterns seem to be not particularly important determinants, unlike the expected patterns for allergens. There is individual difference in susceptibility. For instance, one person may be highly reactive to the fumes of ammonia, ether, perfumes, plastics, turpentine, automobile exhaust fumes and alcohol but not be much affected by gas stove fumes, acetone, floor wax, chlorinated water, or pesticides. Another person may react to all of these agents, whereas a third person may be affected significantly only by the fumes from gas appliances such as the kitchen range. Subjects who had previously reacted clinically to DDT on single blind testing were selected from this group of patients for this study.

Testing Material and Procedure

Crystalline DDT was dissolved in a preservative-free food oil. The final dilution, labeled 0.01 mg. DDT/ml. (10 ppm) was submitted to gas chromatographic analysis and was reported to contain 0.009 mg./ml. of P, P′ and 0.0005 mg./ml. of O, P DDT. The same oil without the DDT served as the control. Test and control solutions could not be distinguished by odor either by the test subjects, by any of the testing personnel, or by 8 other persons who considered their olfaction to be acute. Repeated tests were run by an entomologist and by other personnel who deal professionally with pesticides with failure to detect the DDT solutions.

A double blind pattern of testing appeared to be necessary because we have learned that strong suggestion alone can induce and can alleviate emotional, myasthenic and vascular responses typical of a true chemical reaction in these persons. Our control physician and observer selected either a DDT or control specimen, dipped the end of a glass rod about 1 cm. deep in it, handed the rod to the testing physician and observed its administration to a total of 8 subjects. This rod was held 1 to 2 inches below the nostrils of a subject for a maximum of 6 minutes. Tests were carried out on 3 separate testing days. On the first 2 days only 1 or 2 tests were administered. Three persons served as subjects on more than 1 day. In all, 45 test presentations were made.

The testing physician on the third testing day requested that the first 3 presentations to each patient be controls on a single blind basis to establish a baseline. The control (observer) physician failed to heed this request. On this day we carried out a concomitant study of electromyograms of the deltoid muscle. (The results of this study will be reported separately.) The test specimen was presented to the patient for 5 minutes only on this day, electromyography was carried out with an exercise routine, and in from 2 to 10 minutes another test specimen was presented.

Results

All records and interpretations were sent to the observer physician before identity of test specimens was disclosed. Reactions were scored on the basis of subjective reports by the patients. The cardinal symptoms of immediate reaction were blurring of vision, pulling sensation behind the eyes and at the nape of the neck, dimming of vision, dulling of sensorium, slowing of thought processes, and muscular weakness. Most subjects became withdrawn and quiet.

Five reactions followed 23 control specimens (table 1, chart 1). Thirteen reactions followed 22 DDT specimens ranging from 10 ppm to 10,000 ppm. The weakest testing strength, 10 ppm, was identified somewhat less readily than the higher concentrations. Of 16 tests with 100 ppm DDT or stronger, 10 elicited positive responses. Discrimination between these tests and controls is significant at about the 0.01 level. Although an attempt was made to spare the more sensitive subjects from the effects of exposure to the more concentrated solutions, a dose-effect correlation appears. As shown in chart 2 the proportion of responses to tests made is: controls $^{5}/_{23}$ or 21.7 per cent, 10 ppm DDT $^{3}/_{6}$ or 50 per cent, 100 ppm DDT $^{4}/_{7}$ or 57 per cent, and 1,000 ppm $^{5}/_{7}$ or 71.4 per cent.

Accuracy of 3 individual subjects was particularly good. Subject No. 1 gave 5 correct responses to 5 tests, subject No. 2, 7 correct of 9 tests, and subject No. 6, 5 correct of 6 tests. The total score for these was 8 of 11 DDT identifications and no reaction to 9 controls. No subject produced a score of less than half of the presented specimens identified correctly. Two obvious placebo reactors each correctly identified 1 of their 2 controls.

TABLE 1: Subjective Responses to DDT

Numerals: order of presentation on a given testing day. Letters: E = 10 ppm DDT, D = 100 ppm DDT, C = 1,000 ppm DDT, B = 10,000 ppm DDT

Subject	Control		DDT Tests		
			Reaction		
	0	Reaction	0	Mild	Definite
1	1,2,4			E_3	D_5
2	1,4,6		E_2D_3		$D_5C_7E_8$
2 (earlier date)					E_1
3	5,7	4*	E_1D_2	C_3	C_6
3 (earlier)					D_1
4	4,5	6	C_1E_3	D_2	
5	1,4	5	C_2B_3		
5 (earlier)	1				C_2
6	1,3,5		D_4		C_2B_6
7 (earlier)	1	2			
8 (earlier)	1	2			
	18	5	9		13
Ratio +/total	5/23 = 0.217		13/22 = 0.591†		
Tests 100 ppm or stronger			6		10
Ratio +/total		0.217	10/16 = 0.625‡		

* Included in computations despite assessment by testing physician prior to disclosure that this was a reaction starting in "control" period.

† Statistical difference test and control, confidence level <0.02.

‡ Confidence level: 0.0125.

Statistical Comment

It is, of course, possible that the results shown in table 1 could have happened purely by chance. But since the order of presentation of blank and active doses was actually randomized, it is possible to compute the maximum probability that the subjects could have correctly classified 31 or more of the doses without any clues to assist them.

Under the assumption that no clues are available, the experiment can be seen to be equivalent to the following game:

1. The experimenter prepares 45 opaque envelopes, putting blank slips into 23 of them and marked slips into the remaining 22.
2. The envelopes are shuffled thoroughly by an assistant, out of sight of the experimenter, and then lined up on a table.

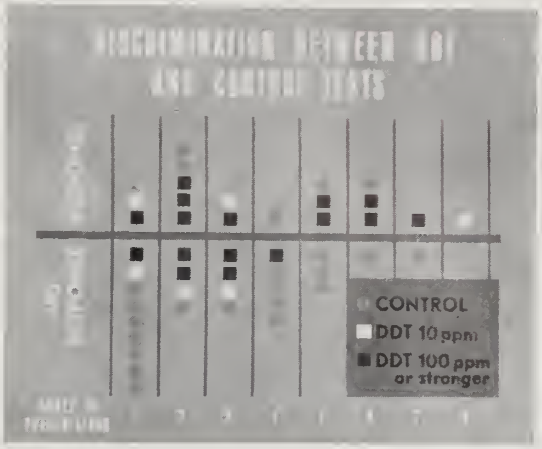

Chart 1

3. Subject No. 1 is asked to classify the first 5 envelopes without examining them in any way, subject No. 2 is asked to classify the next 9, and so on.

Even under these restrictions there are many ways that the subjects might go about classifying the envelopes. For example, each subject could toss a coin for each decision, classifying the envelopes as marked if the coin falls heads and blank if it falls tails. In this case the probability of 31 or more correct classifications is about 0.0001. More generally, the group could decide in advance, by any means that suited them, on a specific order of classifying the envelopes into blank and marked. Since the actual order of the envelopes is by assumption random, it can be shown that the only thing one needs to know about their chosen "strategy" in order to calculate the probability of getting 31

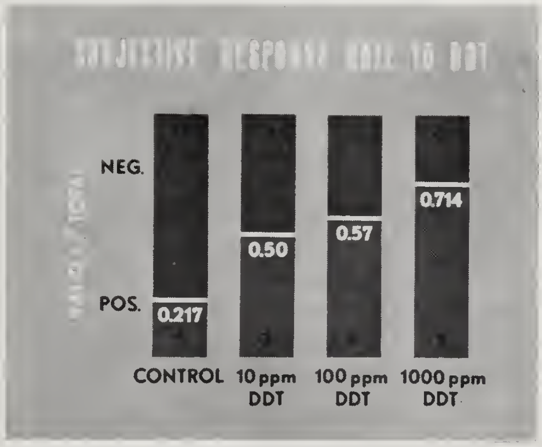

Chart 2

or more correct classifications is the number of cases they decide to call "marked." [2]

If, as it actually turned out, they decide to classify 27 as blank and 18 as marked, the probability of 31 or more correct classifications is about 0.0001. However, they could just as well have decided to call 23 blank and 22 marked. In this case their chance of getting 31 or more right is considerably better, but still does not exceed 0.0125. Since this latter strategy as far as we can determine is the best they can use under the conditions imposed, it appears that the results of table 1 can hardly be attributed to mere chance.

(It should be noted that the test subjects were never assembled as an entire group and that even the testing personnel could not guess the total number of presentations which would comprise this experiment.)

Discussion

In evaluating errors made by subjects in this study there are several factors which should be noted: Responses occurred to higher concentrations of DDT when lesser concentrations did not produce immediate reaction. There is some evidence of cumulative or priming effects from successive exposures to DDT. In 3 instances 10 or 100 ppm produced no response after initial presentation, but these doses did provoke response on subsequent trial. Similarly, subject No. 3 showed a mild response on first exposure to 1,000 ppm, but a definite reaction was provoked by the same concentration administered 40 minutes later. In 8 of the 9 instances in which there was a failure to identify a DDT specimen there was reaction to a later DDT test. On the third testing-day test presentations were made in rapid succession when there was no obvious response to a test. As little as 2 minutes might elapse between the end of 1 test and the start of the next. In some instances the reaction apparently took somewhat longer to develop than we had allowed. It is probably true that 3 of the 5 reactions to controls represent a delayed DDT test response. One of these false positives was called as unsatisfactory by the testing physician prior to disclosure because of a strong suspicion that it represented carry-over from a reaction to an unknown factor starting in the supposed control period. Even so, it is included in the statistics as an "error."

Disclosure after termination of the experiment revealed that the supposed control period was nonexistent and that the patients had received DDT. Carry-over from 1 DDT test to another is also possible. Since controls were as numerous as tests in the later presentations, this factor would not bias the results in favor of DDT tests. Another possible factor should be considered inasmuch as 8 of 9 failures of DDT to elicit a reaction occurred within the first 3 presentations. The testing physician believed that the first 3 specimens were single-blind controls. The occurrence of 3 reactions to what were actually DDT exposures in this period was sufficiently surprising to the testing physician that it is conceivable that her attitude could have influenced the subjects to suppress reactions. This same misinformation probably colored the testing physician's judgment in that small subjective changes were considered to reflect stress or adventitious fumes which must be accepted as the baseline of reference against which test specimens would be judged. In any event, despite this and despite the possibilities described in the first 3 factors, the results of this experiment show ability of the subjects to discriminate between DDT and control solutions beyond a reasonable doubt.

The surface of the rod available for evaporation of DDT was approximately 1 cm.^{2} Exposure was made 1 to 2 inches below the patients' nostrils for not more than 6 minutes. We calculate that from 16×10^9 to 16×10^{12} DDT molecules might be available in the surface layer of the oil according to the dilution. The vapor pressure of DDT is low, only 2.1×10^{-7} mm. Hg at 22°C, and DDT has an affinity for the nonvolatile oil. Thus, the actual dose delivered to the patient's nasal mucosa could not have been more than a relatively few molecules. For perspective, one should compare this with estimations that the average American citizen ingests from 0.1 to 0.2 mg. of DDT daily in addition to other pesticides.[3, 4] Three slices of bacon may legally contain as much as 0.0085 mg. of DDT plus an equal amount of toxaphene and lindane.[5] Both autopsy and biopsy data indicate DDT and DDE levels in 100 per cent of our population, the average fat content for DDT and its metabolite DDE combined being 10.3 ppm (autopsy)[6] and 11.8 ppm (biopsy).[7] This latter figure is put at 12.7 ppm of both chlorinated hydrocarbons expressed as DDT. It is possible that the level of accumulation of fat-stored DDT is a determinant of our failure to induce clinical reactions with concentrations below 10 ppm.

We are here dealing with what appears on the surface to be a different kind and order of toxicity than is seen in the usual experiments with DDT. After oral administration of 300 mg. DDT/Kg. to rats there is a latent period of about 2 hours before tremors and convulsions appear. If the route be intravenous, there is a latent period of 5 to 10 minutes, with the first response being blepharospasm and twitching ears. The intravenous LD_{50} of DDT is 40 to 50 mg./Kg. for rats and 50–60 mg./Kg. for monkeys.[8] This contrasts with responses starting in 20 seconds to 5 minutes and a far greater dose sensitivity in our subjects. In part these differences may relate to the greater awareness of changes in mentation possible in humans, hence an earlier detection of onset of reaction. The nasal route of administration used in these studies favors rapid absorption with direct carriage of the inhaled molecules to the brain. Finally, a toxic dose considered from the standpoint of impaired cerebral functional capacity is not necessarily in the same realm as a lethal toxic dose. Goldfish show behavioral change in water levels of 0.44 mg./ml. toxaphene,[9] and quail and bobwhite show impairment in learning at feeding levels of 20 ppm DDT within 8 weeks.[10]

The subjects of this experiment are a highly selected group. Over the past 4 years more than 50 people with this form of toxic reactions to multiple chemicals have been diagnosed in 1 private allergy practice. The subjects for this experiment are among the more sensitive patients in the hypersusceptible group. It is not possible from any data presently available to determine the incidence of this type of functional impairment in the population. Various degrees of this type of disability exist. Persons affected to a clinically significant degree are, however, certainly not rare, judged from experience here and in the hands of the few other physicians who search for this form of chronic toxicologic illness.[11]

It is important to know whether this is an allergic illness, since this could mean that only a part of our population is at risk. Unfortunately, the evidence is divided. One patient has been followed who reacts to an extreme degree with all the cerebral and muscular manifestations seen in these chemical reactor patients, but she is sensitive to additive-free egg and not at all to the solvents, pesticides, or other chemicals. On the other hand, the very great variety of chemical excitants which affect individual patients are difficult to reconcile with our concepts of an antigen-antibody reaction even though the persons affected do have allergic complaints in addition to their exquisite degree of chemical susceptibility. It is possible that allergic stress predisposes to susceptibility to toxic injury in much the same way that a history of frank toxicologic stress also seems to predispose to this form of illness.

The lipid-solvent and lipid-soluble characteristics of the excitants of chemical susceptibility suggest that the site of injury within the cell may be related to the integrity of intracellular membranes. DDT is found in fat, which in turn in cell membranes is believed to affect cell permeability and cell organization in every cell in the body.[12] The clinical picture of generalized toxic breakdown pattern then might be explained by disruption of such membranes or of a mechanism responsible for repair of these membranes. Cytoplasmic inclusion bodies known as lysosomes contain potentially cytotoxic proteolytic enzymes wrapped in a proteolipid membrane. These membranes are weakened by certain antigen-antibody reactions,[13] by hydrocarbon carcinogens,[14] and by nonionic detergents, to name but a few of the multiple and varied causes of breakdown of lysosomes.

One of the consequences of lysosome destruction probably is stimulation of cell division. We know that rupture of lysosomes is a requirement preceding DNA synthesis and regeneration.[13] We know that phytohemagglutinin, streptolysin-S and staphylococcus filtrate, all of which stimulate lymphocytes to become large blast cells, synthesize DNA and divide, and all unstabilize lysosomal membranes. With this information perhaps we can now understand another characteristic of the female patient who is hypersusceptible to environmental chemicals. Platt and Kailin[15] found that Barr bodies temporarily disappear from the nuclei of both buccal and vaginal mucosa in female chemical reactor patients and reappear when the stress is removed. This probably involves a physicochemical alteration in the DNA material such as would occur in a cell about to enter a mitotic phase. More ominous is the fact that of our first 47 chemical-susceptible patients, 4 who are between 40 and 55 years of age have developed malignancies.

One may ask whether DDT and related pesticides are a primary cause of chemical susceptibility. The answer is probably not, for 3 reasons. First, some affected people gave a history antedating DDT. One of these subjects, a woman in her 40's, recalls feeling dizzy and nauseated in her childhood whenever she was near kerosene lanterns. Second, several victims date the onset of symptoms to other obvious toxic exposures; in 3 instances extraordinary amounts of paradichlorobenzene were involved; in another a refrigerator leaking gas was finally discovered after the patient's malaise had lasted for 6 months. Third, a few patients present a typical clinical picture on exposure to kerosene, utility gas fumes, auto exhaust, and the like, but are not particularly affected by chlorinated hydrocarbons as DDT. These observations indicate that cumulated exposure to toxic substances may be of more critical importance to the etiology of chemical susceptibility than is exposure to a particular kind of chemical.

Summary

Crystalline DDT dissolved in food oil at from 10 to 10,000 ppm when held 1 to 2 inches under the nostrils of highly sensitive subjects elicited in a few minutes visual disturbances, headache, perceptual abnormalities, muscular weakness, and slowed mental and motor activities. The testing solutions could not be distinguished from the diluent by nonaffected persons. In a testing procedure which was essentially double-blind and monitored test subjects differentiated test from control presentations with a high degree of statistical confidence. There was also evidence of dose-correlation. The incidence of cerebral effects from DDT and other elements of the man-made environment is unknown beyond the fact that it is not a rarity. It is suspected that the pathogenesis concerns a breakdown in intracellular lipid-containing membranes.

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The Management of Supraventricular Arrhythmias*†

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The development of the technique of programmed DC electrode shock or cardioversion by Bernard Lown has made it possible to electively convert most patients with supraventricular arrhythmias to normal sinus rhythm.[1] Atrial flutter, which frequently is refractory to quinidine therapy, is almost invariably converted with DC shock and at extremely low current levels. About 90 per cent of patients with atrial fibrillation can be successfully converted to normal sinus rhythm.[2] The results of the experience in the first 124 patients treated at the Duke University Medical Center are listed in table 1. In this initial group of patients 49 per cent had previously failed to convert with an adequate trial of quinidine therapy. The technique used in converting these patients has been previously reported.[3]

TABLE 1: Immediate Success of Conversion of Supraventricular Arrhythmias

Type of Rhythm	Number of Patients	Number Restored to Sinus Rhythm	Per cent Success
Atrial fibrillation	108	100	93
Atrial flutter	16	16	100
	—	—	—
	124	116	94

Complications. Cardioversion was attempted in the 124 patients on 175 separate occasions. There were 7 complications. These included 4 incidences of systemic embolism, fortunately none of which resulted in permanent sequelae. One embolism occurred during the period of amnesia or anesthesia, 1 72 hours after the procedure, and 1 each on the seventh and tenth days after the procedure. Two of these 4 patients had a preceding history of embolism. All of the 4 patients had rheumatic heart disease. Of interest is the observation that 32 per cent of all the patients in this series with rheumatic heart disease also gave a history of systemic embolism. An additional patient developed an area of pneumonitis thought to be due to aspiration. Another patient experienced ventricular fibrillation as a result of premature discharge of the condenser. This potentially serious event was readily converted to normal sinus rhythm with a subsequent shock. One patient demonstrated mild ST-segment depression on the electrocardiogram following the procedure.

Fatalities as a result of this procedure have been reported by other investigators. A review of such events suggests that most of these patients were suffering from digitalis intoxication. It is now generally concluded that the use of cardioversion in such patients is potentially hazardous and should be avoided if at all possible.

Benefits of conversion to normal sinus rhythm. It is well known that most but not all patients with atrial fibrillation, unless adequately digitalized, have a higher resting heart rate than when in normal sinus rhythm. Patients with atrial fibrillation experience during exercise a greater increase in heart rate, even with full digitalization, than they would when a similar level of exercise is performed while in normal sinus rhythm. Therefore, maintenance of normal sinus rhythm tends to prevent an inappropriate rise of heart rate in response to exercise.

There is increasing evidence that a significant number of patients have an increase in stroke output following conversion. Analyses of studies carried out in several clinics indicate that about three-fourths of the patients have an increase in output at rest of 30 per cent or more. Even a higher per cent of patients have an improved stroke output during exercise when in normal sinus rhythm.[4] This improved stroke output is thought to be the result of the restoration of an effective "atrial kick." Braunwald[5] has shown that as a result of the "atrial kick" the same patient may have a higher left ventricular end-diastolic pressure with a lower mean left atrial pressure when in normal sinus rhythm than that present when the patient has atrial fibrillation.

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Third, there is increasing evidence that patients with atrial fibrillation have a higher incidence of systemic and pulmonary embolisms than do patients in normal sinus rhythm. This is especially true in patients with rheumatic heart disease, especially mitral stenosis. It has been demonstrated by Freeman[6] that conversion to normal rhythm results in a decrease in the incidence of embolism.

Maintenance of normal sinus rhythm. There is ample evidence to indicate that sinus rhythm is usually the preferred rhythm if it can be maintained. In order to maintain patients in sinus rhythm after conversion from atrial fibrillation it is necessary to continue medication with an antifibrillatory drug. Quinidine preparations, for the most part, are more successful than synthetic compounds. Not all patients, however, can be maintained in normal sinus rhythm.

In an attempt to establish guide lines to use in selecting patients that are likely to maintain sinus rhythm, 100 patients that were successfully converted to sinus rhythm were followed for periods up to 20 months. It should be emphasized that 60 per cent of these patients had previously failed to attain sinus rhythm with adequate trials of oral quinidine therapy. Therefore, these patients might be considered to have more advanced cardiovascular disease than patients whose rhythm could be converted to normal with oral quinidine. Following conversion, sufficient quinidine was given to maintain serum levels of 3 to 5 mg./L.

The group of 100 patients was shocked 167 times; 69 patients received only 1 shock, and 31 had from 2 to 8 electrical conversions. Pertinent parameters were carefully analyzed to determine what factors might predispose to the maintenance of normal sinus rhythm. In table 2 the patients are separated according to etiologic groups. It can be seen that those patients with pure mitral stenosis are more likely to maintain sinus rhythm than those with multivalvular involvement. It is also apparent that the duration of atrial fibrillation determines in part the success of maintaining normal rhythm following a conversion (table 3). That functional classification is also of prognostic help is demonstrated in table 4.

TABLE 2: Factors Influencing Maintenance of Sinus Rhythm: Etiology of Heart Disease

ETIOLOGY	PER CENT MAINTAINING SINUS RHYTHM (12 months)
Rheumatic heart disease:	
Pure mitral stenosis	78
Multivalvular involvement	47
Miscellaneous	75
Coronary artery disease	45

TABLE 3: Factors Influencing Maintenance of Sinus Rhythm: Duration of Atrial Fibrillation

DURATION	PER CENT MAINTAINING SINUS RHYTHM (12 months)
Less than 1 year	85
Greater than 1 year	36

TABLE 4: Factors Influencing Maintenance of Sinus Rhythm: Functional Classification

FUNCTIONAL CLASS	PER CENT MAINTAINING SINUS RHYTHM (12 months)
I and II	64
III and IV	44

The amplitude of the fibrillatory waves in lead V_1 of the electrocardiogram was not found to be correlated with the success of maintaining normal rhythm. The presence of an abnormal P terminal force[7] or the duration of the P-R interval present following conversion was of no prognostic aid.

The X-ray films of 58 of the total group of patients were evaluated for the size of the left atrium and the transverse diameter of the heart. No specific correlation between these parameters and the maintenance of normal sinus rhythm could be made. However, patients with gross cardiomegaly or a grossly enlarged left atrium rarely maintained normal rhythm.

Therefore, of the factors evaluated, it was found that the etiology, the duration of fibrillation, and the functional classification of the patient were the parameters of most prognostic significance. Ischemic or coronary heart disease, the presence of atrial fibrillation for greater than 1 year's duration, and a functional class III or IV were adverse influences; the alternatives of these, i.e., mitral stenosis or miscellaneous causes of atrial fibrillation, duration of the arrhythmia for less than 1 year, and a functional class I or II were favorable factors.

When one considered the presence or absence of adverse factors it was possible to predict the likelihood of maintaining normal rhythm in a given patient. When no adverse factors were present 86 per cent of the group maintained sinus rhythm for 1 year; when 1 adverse factor was present 78 per cent of the patients remained in sinus rhythm; when 2 were present, 38 per cent maintained normal rhythm for the same period; and when all 3 adverse factors were present, only 33 per cent maintained normal sinus rhythm for 1 year.

Selection of patients. Conversion should not be attempted in all patients. As a result of our experience, patients with atrial fibrillation can be divided into 3 groups: those in whom conversion is contraindicated (table 5); those in whom cardioversion is relatively contraindicated (table 6); and those in whom it is indicated (table 7).

TABLE 5: Contraindications to Electrical Conversion

1. Digitalis intoxication
2. Supraventricular arrhythmia with complete heart block
3. Frequently recurring supraventricular tachycardia
4. Angina pectoris relieved by the onset of atrial fibrillation

TABLE 6: Relative Contraindications to Electrical Conversion

Defer Conversion to a Later Date

1. Recent onset of fibrillation (less than 2 weeks)
2. Candidates for cardiac surgery
3. Immediate postoperative period
4. Supraventricular arrhythmia with hyperthyroidism
5. Recent systemic embolism (within 8 weeks)

Questionable Value

1. Slow ventricular rate without digitalis
2. Quinidine intolerance
3. Two or 3 adverse factors
4. Previous attempts without symptomatic improvement
5. "Benign" fibrillation of long duration

TABLE 7: Cardioversion Indicated

1. Systemic embolism (at least 8 weeks previously)
2. No or 1 adverse factor
3. Congestive heart failure that does not respond to conventional measures
4. Acute cardiovascular decompensation resulting from the arrhythmia

Method of conversion. Once it is determined that the patient should be cardioverted, certain details should be carefully followed. Digitalization to the point that the ventricular rate is adequately controlled is indicated. The drug, however, is omitted for 24 to 48 hours before the procedure. Congestive failure is controlled by conventional techniques. Diagnostic procedures are carried out to determine the etiology of the atrial fibrillation. Maintenance quinidine therapy is given by the oral route for 72 hours prior to the procedure. If conversion occurs spontaneously the drug is continued; if quinidine toxicity or intolerance occurs, the procedure is abandoned and digitalis continued. The patient is fasted overnight prior to the procedure except for the quinidine. Electrical conversion is carried out by a team consisting of an anesthesiologist, who administers light anesthesia or analgesia, an assistant, and a physician familiar with the recognition of cardiac rhythm disturbances. Physical activity is restricted for several hours following successful conversion. If conversion is successful, maintenance therapy with both quinidine and digitalis is continued. Anticoagulation is not employed unless there has been a recent pulmonary or systemic embolism. In such a patient anticoagulation therapy is instituted and continued for 8 weeks prior to conversion.

Summary

Electrical conversion has become the preferred method for managing supraventricular arrhythmias. Our experience with 124 patients managed by this technique is presented. The complications and anticipated gains have been discussed. The factors which most importantly influence the long-range maintenance of sinus rhythm are etiology, duration of the arrhythmia, and the functional cardiac classification of the patient. An outline for selecting candidates for electrical conversion of supraventricular arrhythmias has been presented, and the details of carrying out the procedure have been described.

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(Continued on page 576)

Nonsurgical Treatment of Pulmonary Neoplasm*†

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In a consideration of the nonsurgical management of pulmonary neoplasms, this paper will be concerned with the most common entity, bronchogenic carcinoma. Carcinoma of the lung continues to be a major health problem for which little successful therapy has been devised to date. The overall curative results with surgery continue to be poor, ranging from a 5 to 12 per cent 5-year survival rate. Approximately 60 per cent of patients have inoperable tumors when first seen, and of those submitted to thoracotomy 35 to 50 per cent may be unsuitable for curative resection.

At the present time the most effective methods of palliative treatment for inoperable cases are directed toward stopping the growth and extension of the cancer cells. This can be accomplished to a limited degree with ionizing radiation and or chemotherapeutic drugs. This discussion will include reported studies involving X-ray therapy, chemotherapy alone, or X-ray plus chemotherapy as palliative therapy in patients with bronchogenic carcinoma plus some of those undertaken as part of the coöperative chemotherapy program of the Eastern Coöperative Group in Solid Tumor Chemotherapy. The latter were actively participated in by our colleagues at the District of Columbia General Hospital and the Veterans Administration Hospital, Washington, D.C.

In 1958 Guttmann[1] reported her experiences in the treatment of inoperable carcinoma of the lung with 2,000,000 volt and cobalt 60 irradiation therapy. One-third of the patients considered inoperable at the time of initiation of the study were alive for more than 1 year after the completion of treatment, and 48 survived in a decreasing number for a steadily increasing number of months. At the time of the report 4 patients had survived for a period exceeding 4 years. Most patients were treated with the 2 Mev X-ray unit which was superior to cobalt 60 therapy in this study. Three interesting points were noted:

1. There was no correlation between the clinical response and the extent of X-ray involvement by tumor.

2. There was a better response of squamous-cell carcinoma as compared with carcinoma arising from glandular tissue.

3. In a small number of instances it was possible to sterilize even large carcinomas of the lung with external irradiation.

Bloedorn,[2] reporting on his studies with the use of preoperative irradiation and radical surgery in the treatment of bronchogenic carcinoma, concluded that this method is feasible in some of these patients. The resectability rate after "million volt" X-ray therapy was high in carefully selected cases. He noted that the primary tumor could be "sterilized" and that "sterilization" of lymph-node metastases in mediastinum was also possible. The overall survival of patients, however, was not greatly improved over the untreated controls in the preliminary reports of this study.

There appears to be little doubt that tumor shrinkage may occur during radiation therapy and that relief of symptoms may be effected. However, even when complete "sterilization" of the tumor in the chest occurs the overall survival

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of patients may not be greatly improved. In the past 10 years the Eastern Coöperative Cancer Chemotherapy Group of which we are a participating member has attempted a number of therapeutic maneuvers to influence the course of nonresectable carcinoma of the lung.

In one of our early studies,[3] it was demonstrated that neither nitrogen mustard nor triethylenethiophosphoramide was appreciably effective in carcinoma of the lung that had been previously irradiated. In tumors not previously irradiated one-third of the patients showed a decrease in measured tumor size without any significant improvement in survival times.

In the past 5 years a number of studies involving X-ray therapy and chemotherapy have been undertaken by the Eastern Coöperative Cancer Chemotherapy Study Group. In a previously reported evaluation of nitrogen mustard,[4] X-ray therapy (4,000 rads), and nitrogen mustard plus X-ray therapy (4,000 rads), increased toxicity was demonstrated with combination therapy without influencing survival. When the X-ray dose was increased to 5,000 rads and randomized against a combination of X-rays and 5-fluorouracil or X-rays and actinomycin D, no improvement in survival time could be demonstrated.[5] Since 5,000 rads offered no significant improvement in survival but did increase the toxicity as a result of therapy, the choice of optimal radiotherapy for palliation and tumor shrinkage requires further investigation.

It is conceivable that large doses of X-rays may prevent the demonstration of the ability of chemotherapeutic drugs to sensitize this tumor to the action of ionizing irradiation. If the sensitizing drug and small doses of X-rays prove comparable to large doses of X-rays alone, a decided benefit for treatment time and patient reaction will have been achieved. In addition, if sensitization can be demonstrated we may have available a method of testing the combination of drug and X-ray therapy in an in vivo system. We are currently engaged in a study which will test this hypothesis.[6]

Wolf et al[7] from the Veterans Administration Coöperative Chemotherapy Group studied 554 patients with inoperable bronchogenic carcinoma. Three hundred and eight were given radiation therapy doses of approximately 4,000 to 5,000 r, with mainly mesovoltage radiation (200–260 kv.), whereas 240 similar patients serving as controls were given an inert compound. The median survival of patients given radiotherapy was 142 days, as compared to 112 days for the control group. Twenty-five per cent of the patients who had the longest survival after radiation lived at least 307 days, as compared to 233 days for the best 25 per cent of the control group. There was no correlation between local roentgenographic response of the tumor and the survival. The survival curves were farthest apart at the end of the ninth month, and at the end of the first year 18 per cent of the patients treated were still living as compared to 14 per cent of the control group. According to the cell type radiation had no apparent effect in prolonging the lives of the patients with anaplastic small-cell carcinoma, but the patients with adenocarcinoma and squamous-cell type were slightly more responsive.

In another report from this same group[8] 296 patients with bronchogenic carcinoma treated with nitrogen mustard were compared to 327 patients treated with placebo. The study concluded that there was no difference between the 2 groups in terms of survival beyond 12 months. It was also shown in a third study[9] that cortisone had a deleterious effect on patients with cancer of the lung and was associated with a shorter survival time as compared to the placebo group.

In clinical trials with alkylating agents and antimetabolite drugs as palliative agents in the chemotherapy of lung cancer sporadic instances of benefit have been described.[6] No significant influences upon survival have been associated with these palliative responses.

Observations that methotrexate given every 4 days was effective in the treatment of acute lymphocytic leukemia in children whose advanced disease was returned to early disease by pretreatment with vincristine and prednisone led Ross and Selawry[10] to undertake a pilot study of methotrexate with this schedule of therapy in ambulatory patients with inoperable bronchogenic carcinoma. Their results have suggested that both 50 per cent regression of tumor size and survival time can be increased by this regimen of therapy. Extensive studies evaluating these results are in progress.[6]

For the palliation of recurrent pleural effusion, several agents can be given by the intrapleural route: mechlorethamine, 5-fluorouracil, Cytoxan®, or Atabrine®.[11, 12] The effectiveness of these compounds compares favorably with those obtained with radioactive gold (Au 198).[6, 9]

Specific complications such as local pain, especially if it is due to involvement of ribs, spine, pleura, or pain due to remote metastases in bone can be relieved by radiotherapy.[13] The superior vena caval syndrome may respond favorably to radiotherapy or chemotherapy.[6]

In continuing attempts to determine the best available palliative therapy for carcinoma of the lung, studies are in progress with the use of newer chemotherapeutic agents,[14, 15] on revised dosage schedules for old chemotherapeutic agents, and on other combinations of chemotherapeutic drugs and X-ray therapy.[16] The results of these investigations may improve the management of the patient with advanced bronchogenic carcinoma.

Summary

The management of advanced inoperable or recurrent bronchogenic carcinoma still poses a problem to the attending physician. X-ray therapy, chemotherapy, or combinations thereof may produce subjective and/or objective responses in a limited number of patients but appear to have little effect upon survival. Specific complications such as pain or superior vena caval syndrome may respond to X-ray therapy or chemotherapy. New clinical trials involving new agents, revised dosage schedules, and combination therapy are in progress and may improve the prognosis for these patients.

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New Recommendations on Typhoid Immunization

Surgeon General William H. Stewart of the Public Health Service states that routine typhoid immunization is not recommended in the United States. His statement is based on findings of the Public Health Service Advisory Committee on Immunization Practices. Text of the recommendations were released, July 29, in the *Morbidity and Mortality Weekly Report* for the week ending July 23. The Report is published by the Communicable Disease Center in Atlanta, Ga.

The Committee, composed mostly of experts from without the Service, recommended selective immunization in the following situations:

1. Intimate exposure to a known typhoid carrier as would occur with continued household contact.
2. Community or institutional outbreaks of typhoid fever.
3. Foreign travel to areas where typhoid fever is endemic.

The Advisory Committee stated further, "Although typhoid vaccine has been suggested for individuals attending summer camps or those in areas where flooding has occurred, there are no data to support the continuation of these practices."

The incidence of typhoid fever in the United States has declined steadily for many years. At the present time less than 500 cases are reported annually, and a continuing downward trend can be expected. Cases are sporadic and are primarily related to contact with carriers rather than to common source exposure.

Referring to vaccines for paratyphoid A and B, which are typhoid-like fevers, the Advisory Committee stated, "The effectiveness of paratyphoid A vaccine has never been established, and recent field trials have shown that available paratyphoid B vaccines were ineffective. In view of these data and recognizing that paratyphoid A and B antigens when combined with typhoid vaccine may increase the occurrence of vaccine reactions, use of paratyphoid A and B vaccines is not recommended."

Fertility Control—Temporary or Permanent?

A. GRACE PIERCE, M.D.*

In the past few years there has been increasing recognition of the desirability and necessity for birth control. Population control programs in some countries are now being given top priority consideration. The logic of this arises out of the fact that the welfare of nations hinges on socioeconomic factors directly related to population trends. Unique problems associated with underpopulation or overpopulation of an area or nation have been witnessed throughout history. Currently many nations are experiencing extreme pressures for survival because of their "population explosion." Here in the United States we have been fortunate so far in that development and industrialization have been able to grow in advance of our population. However, a look to the near future and an appraisal of the past indicate that an apathetic approach to population control could spell disaster for all of us.[1]

With the advent of oral contraceptive drugs and the presently innovated intrauterine contraceptive devices conception control has become a greater reality than heretofore known. This undoubtedly has been due to the ease in methodology, with the attendant high degree of patient acceptance and effectiveness.[2] Since the ultimate value of any method of contraception depends upon patient acceptance, it quite naturally must follow that the patient should be afforded reasonable latitudes in choice of method to be used.[3] When a patient presents herself initially as a candidate for contraception, evaluation of the case at hand must be individualized. It is here at this point that a determination should be made as to whether suspension of fertility should be "temporary" or "permanent." Anything short of an operative procedure, or destruction of the organs necessary for reproduction (as by radiology) must be categorized as "temporary" control.

Prior to a patient availing herself of "permanent" fertility control there must be adequate consultation between the patient and knowledgeable personnel. Even on a strict voluntary basis the patient must be made aware of the full implications of the proposed procedure through "informed consent." "Voluntary sterilization is legal in all 50 states, with restrictions as to the reasons for which it is performed in only 2 states, Connecticut and Utah, and certain conditions spelled out in laws recently passed in Virginia and North Carolina." [4]

There have been discriminatory practices in the use of tubal ligation as a method of birth control. Innumerable patients already overburdened by unneeded and perhaps unwanted pregnancies have been denied this operation. Local medical and community authorities have dictated conditions to be met prior to permitting and executing this procedure, often in a highly inconsiderate and inconsistent way.

Presently the enrollment of millions of women in clinics offering birth control information have overtaxed available facilities and ancillary medical manpower. The majority of these patients are receiving oral contraceptives. Many clinics are prescribing this method almost exclusively, and understandably so in view of ease of administration and great effectiveness. However, the popularization of the use of these hormones in a large segment of the population does not relieve the medical community of the responsibility as to the question of safety. In fact, such overwhelming use of these drugs promotes and accentuates the problem of safety. There are certain unanswered questions about these agents, particularly pertaining to the very long-term and continuous use of hormones. Undoubtedly some of these questions of safety will remain unanswered for several more years.

It is now demanding upon the scientific community to inquire into the logistics of pursuing "temporary fertility control" in great masses of women when "permanent fertility control" is the realistic desire of the patient and the community. From a public health standpoint the continued use of these steroids as the patient

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ages probably has some decreasing factors of safety. Until there are definite answers as to potential hazards[5, 6, 7] (e.g., hepatotoxicity, intravascular thrombosis) in the older aged female only limited investigational use of these steroids should be permitted.

Once a patient becomes a candidate for "permanent fertility control," continuous use of temporary measures should be abandoned for a permanent procedure. Only by this approach can needless medication and possible medical risks through the premenopausal, menopausal, and postmenopausal years be eliminated. If a patient pursues oral contraception into the premenopausal age range, she necessarily must continue with contraception of one type or another well into the postmenopausal years to be "guaranteed" not having a pregnancy occur at age 50. Certainly, if such a patient had satisfied her family desires at the age of 30 or 35, a sterilizing procedure then could have eliminated 15 or 20 years of medication and the possible adverse effects. If it is decided to discontinue oral contraception for a trial period to determine if the patient has actually become menopausal, a substitute contraceptive measure would be necessary for at least several months.[3] It would have to be a very reliable and a very acceptable method or there could be a surprising upsurge in the number of "menopausal babies." Such a reliable and acceptable method currently is not available for mass use. Consequently, switching from oral contraception to another method could put a large number of women "at risk" of pregnancy and in the "high risk" group due to age alone, from a maternal health standpoint.

Of course, advocates for treating all menopausal women with endocrine preparations, regardless of whether or not there are subjective or objective symptoms indicating therapy, will see no reason why oral contraceptives should not be used in managing all patients at all ages. Here again, until controlled studies have demonstrated the long-term safety in universal use of these agents in the older age-group only investigational use should be permitted.

Admittedly, the cost of hospitalizing a patient for the few days required to accomplish permanent fertility control by tubal ligation exceeds the cost of a clinic visit for administration of an oral contraceptive drug or the insertion of an intrauterine contraceptive device. The number of return visits to the clinic, ideally in any of these instances, would average out about the same over many years, since every female should have a routine pelvic examination at least once every 6 months. However, the additional cost of continuous medication for years represents a price differential of some degree. With the intrauterine device this cost is quite negligible. The area of greatest concern from an economical viewpoint probably should be the added financial burden of possible unwanted or unplanned pregnancies. A certain percentage of women ultimately lose interest in taking medication regularly. Without conscientious and continuous application of the cyclic medication there is a breakdown in fertility control. Perhaps such a resultant unplanned pregnancy would serve as a greater stimulus to subsequently following a regular medication schedule, but the "damage" by that time has been done. Had permanent fertility control been accomplished such added inconvenience would have been eliminated.

The overall expense of an unplanned pregnancy must also include an estimate of the cost of such an "economic breakdown" in family planning. Limited income families tend to gear their living conditions to a level that is maximum for that income. An increase of an additional unplanned child could financially embarrass a family to such a degree as to necessitate an overall downgrading in the standard of living for that family. This automatically will serve only to defeat one of the prime objectives of family planning.

In summary, it can be said that family planning is not only desired but mandatory. Our socioeconomic welfare is dependent upon an intelligent application of the available methods of contraception. Classification of candidates for conception control must be categorized into those desiring "temporary" or "permanent" fertility control and then accomplishing this end point by the appropriate method. To persist in using temporary measures for fertility control once a patient has become a voluntary candidate for a permanent procedure can cause serious socioeconomic breakdown in the overall program of family planning and needless patient exposure to potential medical hazards.

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(Continued on page 576)

A Look at the D.C. Public Health Child-Guidance Clinic

CHARLES H. TROSHINSKY, M.D.*

Since Healy's pioneer work in the early 1900's child guidance services have changed in many ways. And yet, certain basic concepts have not. One of these is that a child's emotional growth is most significantly affected by the interaction between him and the adults rearing him. What the child guidance movement did, and still does, is to act on this knowledge by treating (i.e., work with) both child and his significant caretakers.

In a way, this concept was a forerunner of much of what we regard as community psychiatry today, in that community psychiatrists work with the caretakers of their patients, as well as the patients themselves, using the concept that both have an effect on each other. In this light, schools, courts, jails, industries, employers, and government can all be seen as caretakers and thereby have varying degrees of influence on the mental health of their charges.

One of the advantages of a city-supported child-guidance clinic, such as the one I have been associated with for the past 2 years (P Street Clinic), is that the City, being public-health oriented, supports the fact that a professional hour spent with a group of teachers has a far healthier influence than 1 hour spent with an individual patient but recognizes that both are needed.

Evolution of the Types of Services to Fit the Needs

The child-guidance service, for the most part, has been very useful to the child whose parents have within their value system a concern with and an investment in the welfare and future of their child. I should point out that family income has relatively little to do with this value system.

However, the child-guidance services can be of almost no use when the child's parents or caretakers have little or no investment in him. This is primarily because the same lack of investment, besides being devastating to the child in its own right, keeps the parents from using the child-guidance service.

It became obvious to us at the P Street Clinic that if we were to be of use in helping neglected children we would have to go to the children rather than to depend upon their parents bringing them to us. As a result of this thinking we conduct group therapy for young adolescents in a deprived neighborhood junior high; we consult regularly with a group of preschool nursery personnel working for deprived neighborhood children; we meet regularly with teachers of a deprived neighborhood elementary school. The goal in all of this work is to create a healthy emotional atmosphere between the other important caretakers of children whose parents cannot or will not invest themselves. The value of this work cannot be overestimated; at the same time it is almost impossible to assess scientifically, at least at present. A step toward evaluating results of such activities is the development of a follow-up system both for individual patients receiving individual help and for agencies receiving consultation.

One of the exciting aspects of working at the Child Guidance Clinic at this time is to be able to take part in the changing concepts and methods that are evolving. At the same time, we recognize a natural phenomenon that is taking place which concerns us.

Because the "old traditional ways" have not proved useful in meeting the needs of all the children who are troubled, there have been some who advocate "throwing out the baby with the dirty bath water." One result of this is that the training of professional people in the field is being minimized, and some even advocate using deprived individuals without adequate supervision and training to meet other deprived individuals' needs. Those who have acted hastily in this concept have watched well-meaning programs become chaotic. If it is true that a mother cannot give of herself to her own child without having been given to, it is certainly more true that a deprived adult or young adult has to have his needs met before being able to help another.

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Child Guidance as an Instrument of Prevention of Mental Illness

One of the motivations for establishing the child-guidance movement was the belief that the clinic would prevent eventual state hospital admissions of adults by treating them in their childhood. This turned out to be a disillusionment because many of the state-hospital-destined adults came from families who were the least likely to use the clinic services. However, luckily, this pioneering motivation for prevention still permeates the child-guidance field, and other ways of prevention are being sought.

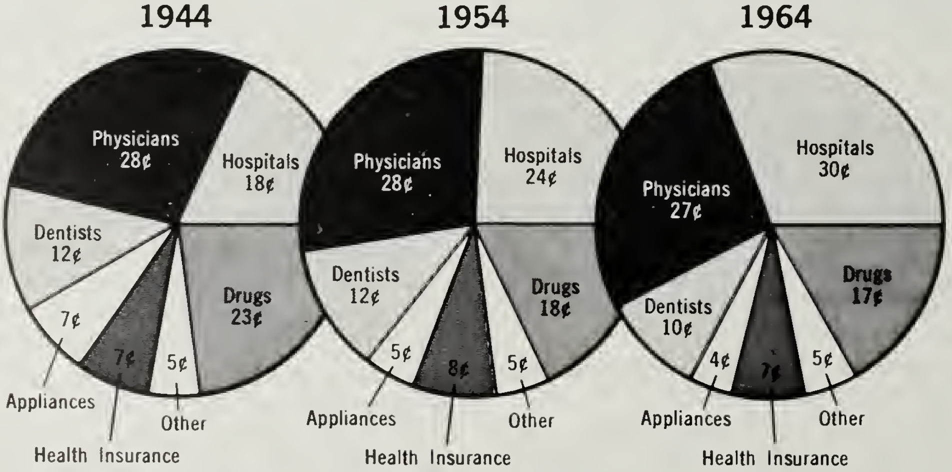
Prevention of mental illness is being carried out by the progressive birth control programs, as exemplified by the District of Columbia Department of Public Health. A child born to a mother who is unable to care for him in a city which is unable to provide a home is quite likely to develop severe mental and/or social illness. Other programs of primary prevention, such as counseling of pregnant women who are most likely to have difficulty accepting their children, intrigue professionals in the child-guidance field.

Our Clinic has learned to recognize that we are quite limited in what we can do alone. Without the help of important institutions of child development (such as the school system), prevention of mental illness will always be an illusory goal. For example, as much as 25 per cent of the children we evaluate have specific learning problems; many of these have minor brain damage which prevents the child from experiencing the success of mastery. This inevitably results in a child having poor self-esteem to the point perhaps of not being able to provide for himself, or at least to the point of not fulfilling his potential. If the schools do not provide specially trained teachers and special education classes the community will spend many times the cost of such provisions in both loss of potential and the undoing of the damage done.

Summary

Some thoughts on the changing child guidance services and concepts have been presented. Child-guidance services have extended their basic concept of working with significant caretakers of the child to the community, both as a more far-reaching way of helping children and as an attempt for primary prevention of mental illness. Some of the activities of the P Street Clinic have been described.

DISTRIBUTION OF THE HEALTH CARE DOLLAR
FOR YEARS 1964, 1954, AND 1944



SURVEY OF CURRENT BUSINESS, November 1965, Vol. 45, No. 11
SOURCE: U. S. Department of Commerce, Office of Business Economics, pp. 20-23. (Calculations by Department of Economics, AMA)

—AMA News Graphichart

Desquamative Interstitial Pneumonia

Report of a Case of a Recently Described Entity*

ROSCOE C. YOUNG, JR., M.D.†, MARVIN A. JACKSON, M.D.‡, AND HENRY D. BELL, M.D.§

DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP) is a chronic pulmonary disease of obscure etiology that possesses distinctive X-ray, physiologic, pathologic, and possibly prognostic characteristics that permit its recognition and description as a clinicopathologic entity.

Originally designated by Liebow[1] as "desquamative histiocytic interstitial pneumonia" (DHIP) because the implicated cells were thought to be histiocytes, subsequent closer study revealed them to be granular pneumocytes instead. Liebow, Steer and Billingsley[2] redesignated the entity "desquamative interstitial pneumonia (DIP)" in their description of 19 cases in September, 1965. Gaensler, Goff and Prowse[3] described 12 cases in January, 1966, and recently Steinberg[4] reported 3 additional cases. Two of the writers were fortunate enough to have personally reviewed Liebow's cases.||

Report of Case

K.P. (FH No. 260-761) is a 45-year-old Negro female social worker whose present illness began insidiously in October, 1964, when she noticed easy fatigability. Three months later she developed progressive dyspnea on exertion (now grade III¶) and cough productive of scanty mucoid sputum. She had an acute episode of "bronchitis" in October, 1965 followed by a 'hot' feeling in the chest. She was placed on penicillin and tetracycline by her private physician but failed to respond. On January 10, 1966 she was admitted to Freedmen's Hospital. She has smoked 1½ packages of cigarettes daily from 1945 to the present. Her only chemical exposure has been to household insecticides. She stated that she had had tuberculous contact, "pleurisy" in 1963 and 1964, and pneumonia in 1937 and 1963. There is a family history of coronary artery disease.

She was a moderately obese, normotensive (140 systolic, 80 diastolic), afebrile (98.6°F) female with bibasilar crepitant, inspiratory and expiratory rales, and an occasional wheeze. There was no evidence of clubbing or cyanosis, and the remainder of the examination was negative. An intermediate strength PPD was read as showing 30 mm. induration with central necrosis; the histoplasmin skin test was negative after 48 hours.

The white blood cell count on admission was 11,000 cells per cu. mm. with 1 per cent basophils, 4 eosinophils, 2 stab forms, 53 segmented forms, 38 lymphocytes, and 2 monocytes. The hemoglobin was 13.6 Gm. and the packed cell volume 40 per cent. A fasting blood sugar was 76 mg., and the blood urea nitrogen was 6 mg. per 100 ml. Serum electrolytes revealed chlorides to be 106 mEq./L, potassium 4.5 mEq./L, and sodium 140 mEq./L. Urinalysis was negative. A gram stain of the sputum revealed gram-positive diplococci and gram-positive cocci in chains and clusters. A serologic test for syphilis (VDRL) was nonreactive.

An electrocardiogram taken on January 11, 1966 was "within normal limits." A gastrointestinal X-ray examination revealed "possible ulcer on the lesser curvature of the antrum and a scarred duodenal cap." A chest X-ray film on the same date revealed a bilateral "ground glass" infiltrate obscuring both lung bases. The upper ⅔ of the lung fields were clear (figure 1).

Lung function studies were performed on January 18, 1966. Results are given in table 1.

Studies show hyperinflated lungs without airway obstruction. This is evidenced by the increase in residual volume and functional residual capacity, increased residual volume/total lung capacity ratio, normal-timed vital capacity, and air velocity index. She had

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|| Postgraduate course—Pathology of the Lung, at Yale University School of Medicine, March 15-20, 1965.

¶ Clinical grades of dyspnea: I, dyspnea on climbing hills or stairs; II, able to walk a mile at own pace but unable to keep pace with a normal person on the level; III, dyspnea on walking 100 yds. or for a few minutes even on the level; IV, dyspnea on slight exertion such as dressing or talking (NTA classification).

TABLE 1: Pulmonary Function Tests

LUNG VOLUMES

Test	Normal	Patient	Patient % Normal
Inspiratory capacity	2270 ml.	1810	80
Expiratory reserve volume	1140 ml.	480	42
Vital capacity	3410 ml.	2290	67
Residual volume	1780 ml.	2630	148
Total lung capacity	5190 ml.	4920	95
Residual volume/total capacity	34 %	53	
Functional residual capacity*	2930 ml.	3110	107
Dead space (Anatomical) (Measured)	176 ml.	176	

VENTILATION

Test	Normal	Patient Air	Patient O_2
Respiratory rate (Rest)	16–20/min.	48	34
Respiratory depth (Rest)	0.5 L	0.426	0.280
Respiratory min. volume (Rest)	6–8 L/min.	20.5	9.52
Alveolar ventilation (calculated from anatomical dead space)	4–6 L/min.	12.0	3.5

DISTRIBUTION OF INSPIRED GAS AND BLOOD

Test	Normal	Patient Air	Patient O_2
Alveolar gas uniformity (% N_2 increased 750–1250 ml.)	<2.0%	4.0	
N_2 elimination rate (% N_2 after 7′O_2)	<2.5%	6.1	

DIFFUSION AND GAS EXCHANGE

Test	Normal	Patient Rest
Diffusing capacity† (carbon monoxide)	28 ml./min./mm. Hg	9 (31%)
O_2 cost of breathing	2–4 ml.O_2/L vent.	6.7
RQ	0.8	1.05
O_2 consumption	200 ml./min.	357
CO_2 elimination	250 ml./min.	376

ARTERIAL BLOOD

Test	Normal	Patient Air	Patient O_2	Patient Exercise‡ 350 Kg/m/m
O_2 content (total)	air-20.6 vols. % O_2-22.9 vols. %	14.0		
O_2 capacity	20.9 vols. %	14.6		
O_2 saturation	96–99%	96		
O_2 tension§	air-95 mm. Hg O_2-673 mm. Hg	76	541	56
CO_2 tension§ (measured)	38–42 mm. Hg	16	21	19
pH	7.38–7.42	7.45	7.39	7.30
CO_2 content (whole blood)	20.5–23.1 mM/L	17.1		

MECHANICS OF BREATHING

Test	Normal	Patient
Maximum expiratory flow rate (200–1200 ml.)	500 L/min.	150
Maximum inspiratory flow rate (200–1200 ml.)	400 L/min.	171
% Vital capacity in 1″	81%	84
% Vital capacity in 3″	95%	100
M.B.C.	94 L/min.	58.3(62%)
Pulmonary compliance	0.12–0.15 L/cm.H_2O	0.091

* Open circuit method.

† Breath-holding method.

‡ 3-minute step exercise test.

§ Measured polarographically.

marked hypoxemic stimulus to ventilation as shown by marked hyperventilation at rest while breathing room air; this was abolished by breathing 100 per cent oxygen (figure 2).

In addition, she had uneven distribution of inspired air as shown by the abnormal test of alveolar gas uniformity and abnormal 7-minute nitrogen clearance. A defect in diffusion of gas is shown by the fall in arterial oxygen tension on exercise and is confirmed by finding her diffusing capacity to be only ⅓ of predicted normal. Her lungs were stiff as shown by the restrictive spirographic pattern and confirmed

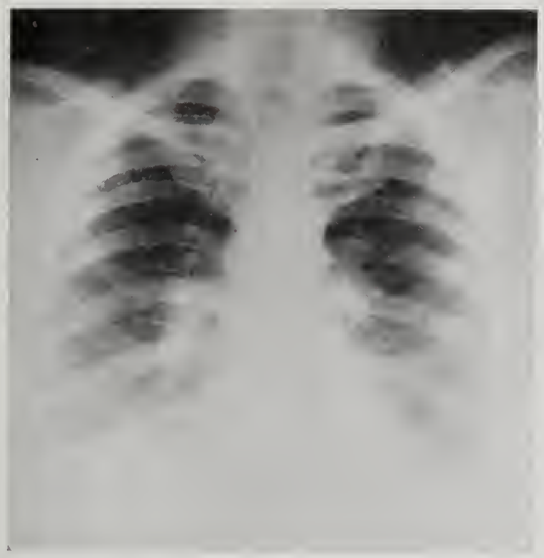


FIG. 1. Admission film showing bibasilar "ground glass" infiltrate partially obscuring both hemidiaphragms. Note that upper lung fields are clear.

by finding decreased lung compliance. These mechanical abnormalities caused her oxygen cost of breathing to be twice that of normal. She had an absolute shunt shown by her arterial oxygen tension which failed to rise normally during 100 per cent oxygen breathing for 20 minutes. This shunt, while she was breathing 100 per cent oxygen, amounted to about 9 per cent of her cardiac output (normal, less than 3 per cent).

Bronchoscopy was performed on January 21, 1966. The tracheobronchial tree appeared grossly normal. A bronchial biopsy revealed "mild chronic nonspecific inflammation." Culture of the bronchial secretions obtained during examination yielded alpha hemolytic streptococci and Neisseria species. Open lung biopsy of the right lower lobe was performed on January 27, 1966; specimens were taken at that time from the superior segment of the right lower lobe and from the lateral basal segment of the right lower lobe.

Grossly, the external surfaces of both specimens were reddish-brown and somewhat granular. The surfaces of the cut sections were reddish-brown. Microscopically, the architectural pattern was generally well preserved (figure 3). There was moderate thickening of alveolar septa by fibrous connective tissue. The most striking feature was the luxuriant proliferation of lining pneumocytes with desquamation into the distal air sacs. These cells were of a very large size with moderately abundant eosinophilic cytoplasm which was finely vacuolated in areas and contained yellowish-brown pigment. Some of the cells were

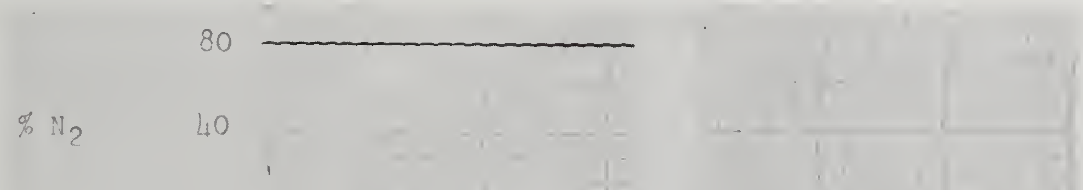
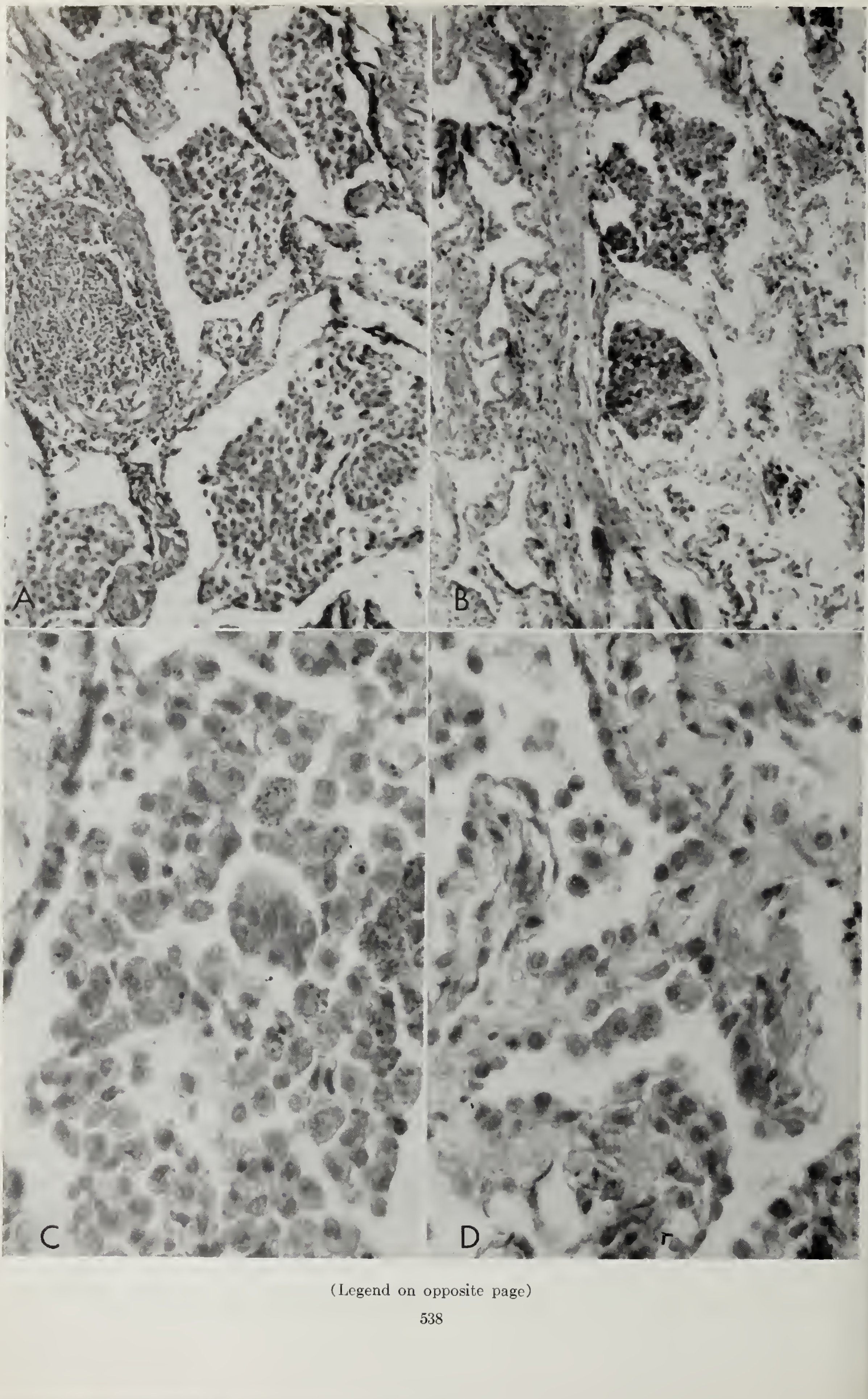


FIG. 2. Polygraph demonstrating ventilatory response to hypoxemia. From above downward, end tidal nitrogen (per cent N_2), 1-second timer, end tidal carbon dioxide (per cent CO_2) and air flow measured at the mouth. A. Patient seated breathing room air. B. Patient breathing 100 per cent oxygen. Note increase in per cent CO_2 and slowing of respiratory rate and flow.



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multinucleated. Admixed with the desquamated pneumocytes were scattered lymphocytes. In addition, there were nodular collections of lymphocytes within the thickened alveolar septa. The medium-sized vascular channels showed moderate hypertrophy of musculature. There were rare foci of "emphysema." Periodic acid Schiff (PAS) stain showed the desquamated pneumocytes to be strongly PAS-positive. Turnbull blue stain showed a few pneumocytes to be iron-positive. Some sections showed great proliferation of epithelia of terminal bronchioles with extension into the surrounding tissue from canals of Lambert. Reticulum stains showed an increase in argyrophilic reticulum in alveolar walls. No corpora amylacea were seen.

The patient was discharged to follow-up care by her private physician on February 21, 1966. Medications consisted of magnesium trisilicate aluminum hydroxide gel and, initially, prednisone 40 mg. daily which was reduced to a maintenance dosage of 10 mg. daily for 1 month. Despite the fact that she has not taken her medications regularly and has not kept her appointments faithfully, her dyspnea has decreased to grade II. Her latest chest roentgenogram, on April 18, 1966, has shown some improvement when compared with those taken January 18 and March 18.

Discussion

Clinical aspects. DIP is a disease of unknown etiology. There are suggestions, however, that it may be caused by a virus. The acute respiratory symptoms that occur during the course of the illness, as in our case, and the finding of intranuclear inclusion bodies in alveolar cells in other cases suggest a viral etiology.[2, 3]

Generally the disease occurs in the third and sixth decade of life. The incidence is only slightly higher in males than in females. Dyspnea on exertion is the most common symptom and usually the presenting one. Cough is commonly nonproductive but is rarely productive of mucoid sputum. Still more rarely is it associated with hemoptysis. Patients may have pleuritic pain. The episodes of "pleurisy" years earlier may well have been the presenting complaint. Gaensler[3] emphasized the pleural complications that can occur in DIP. Fatigue was an early complaint and may be seen in about one-third of the patients. A few of the patients lose weight. One of Steinberg's cases had upper abdominal pain, but no further information was given.[4] The most common physical finding is bibasilar crepitant rales, and this is seen in about 50 per cent of the patients. Cyanosis and clubbing are seen occasionally. Clinically there is nothing distinctive that helps differentiate DIP from other diffuse infiltrative lung disease. The characteristic X-ray picture is a bibasilar ground-glass infiltrate which is seen in about two-thirds of all cases (figure 1). The converse, however, is not true. We have seen several patients with sarcoidosis without hilar adenopathy and basal infiltrates. A very strongly positive tuberculin reaction makes consideration of sarcoidosis less tenable. Liebow and Gaensler remind us that the chest X-ray film may be misleading because pathologically the entire lung is involved. We confirmed this by finding pathologic involvement in the superior segment of the lower lobe when the corresponding location on a chest X-ray film showed no involvement. None of Steinberg's cases had characteristic chest X-ray films.

Pulmonary function aspects. Hyperinflated lungs without airway obstruction may be related to dilatation of air spaces representing honeycombing. Gaensler has shown that DIP, like other types of interstitial pneumonia, may ultimately progress to the "end-stage lung." An increase in the RV/TLC ratio denotes hyperinflation. Our patient had a ratio of 53 per cent (her predicted normal was 34 per cent). Three of Liebow's patients had an RV/TLC ratio in excess of 36 per cent, but none had a value as high as our patient. The increased RV/TLC ratio is due to an increase in the residual volume equal to or greater than 120 per cent of predicted value, but Gaensler's cases all had decreases in residual volume. The normal-timed vital capacity and air-velocity index rule out airway obstruction. All of Gaensler's patients had normal 1-second-timed vital capacities. This value was low in all but 4 of Liebow's cases. Since they showed no other signs of airway obstruction, the low value may have been due to submaximal effort. Why minimal hypoxemia (low oxygen tension at rest as well as on exercise) should cause such a large ventilatory stimulus is unknown. Our patient had marked hypoxemic

FIG. 3. A. Masses of desquamated pneumocytes in distal air spaces. Fibrous thickening of septa. Nodular lymphoid aggregate in septum. Hematoxylin and eosin stain. B. Periodic acid-Schiff (PAS) positive material in cytoplasm of desquamated pneumocytes. PAS technique. C. Mono- and multinucleated desquamated pneumocytes with cytoplasmic vacuoles, PAS-positive material and PAS-negative granules. PAS technique. D. Distal air spaces showing proliferated lining pneumocytes containing cytoplasmic vacuoles and granules. Fibrous thickening of septa. Hematoxylin and eosin stain.

stimulus to respiration because her alveolar ventilation fell from 12 L/min. at rest breathing room air to 3.5 L/min. while breathing 100 per cent oxygen. Hyperventilation at rest is a common finding in all infiltrative diffuse lung disease. Gaensler mentioned that in DIP oxygen breathing shows that "ventilation is stimulated by hypoxemia." Ventilatory response to 100 per cent oxygen follows this thesis. It is tempting to speculate an increase in chemoreceptor sensitivity to hypoxemia because of the minimal decrease in arterial oxygen tension at rest. The mechanism of hyperventilation in other lung diseases is probably reflex. Whether there is inactivation of stretch receptors in stiff lungs as we propose occurs in sarcoidosis[5] or an increase in number of stretch receptors in lungs and respiratory muscles as suggested by Lourenco[6] is open to question.

In DIP, the diffusing capacity is uniformly low regardless of the method used. It is difficult to understand how the minimally thickened alveolar walls in DIP can account for such severe decreases in D_L. Although we did not assess ventilation/perfusion ratio, the major contribution to a low D_L is most likely uneven matching of gas and blood.[7] The finding of absolute shunt is common, being seen in 7 patients in Gaensler's series. Proliferating alveolar cells fill alveoli which are not ventilated and fail to increase their oxygen tension even when the patient breathes 100 per cent oxygen, thus explaining the shunt-like effect. Restrictive lung disease is responsible for the spirographic pattern, decreased compliance and increase in oxygen cost of breathing.

Klaus[8] correlated the presence of granular pneumocytes containing lamellated bodies in normal mammalian lungs with the presence of surface active phospholipid responsible for alveolar stability. These considerations may account for the relative infrequent occurrence of atelectasis in these patients, suggesting to us that the abundance of proliferating pneumocytes may lead to higher phospholipid synthesis and turnover in the lungs of patients with DIP.

Pathologic aspects. DIP shows a microscopic picture of monotonous uniformity of large alveolar cells without pleomorphism but with large nuclei. The electron microscope shows lamellated bodies in the cytoplasm that characterize granular pneumocytes. Because of them the cytoplasm stains PAS-positive.

Steinberg[4] notes the presence of corpora amylacea in some lung sections. These cells may take up small amounts of iron or perhaps a small amount of lipid, as can be demonstrated by the appropriate stain. The air spaces are normal, usually with very little revision of architecture, and lymphoid follicles may be numerous. Usually, more than the normal number of mitoses are seen in high magnifications. Alveolar septa may be thickened, but the thickening is not as marked as in other interstitial pneumonias. Giant cells are occasionally seen. There is an increase in argyrophilic reticulum in alveolar walls that are thickened. Liebow[2] and Steinberg[4] have given criteria for the pathologic differential diagnosis of DIP from other chronic diffuse lung disease.

The importance in being able to differentiate DIP from the usual interstitial pneumonias is stressed because of the reported better prognosis in adrenal corticosteroid treated cases of DIP. Open lung biopsy in diffuse disease of the lung is therefore necessary.[9] Gaensler, however, suggests caution in interpreting optimistic reports on the good response of DIP to steroid therapy. In our patient the unrelated finding of possible peptic ulcer disease may contraindicate corticosteroid therapy, compounding the frustrations of management.

Summary

A case report of a recently described entity of unknown etiology, desquamative interstitial pneumonia (DIP), has been reported. There are characteristic X-ray, physiologic, and pathologic findings. X-ray films show a bibasilar "ground-glass" type of infiltrate which, although characteristic, is not pathognomonic. Pulmonary function tests show restrictive lung disease with hyperinflation, hyperventilation, and diffusion abnormalities. There is a striking hypoxemic stimulus to ventilation. Pathologically, microscopic sections show a monotonous proliferation of large granular pneumocytes into air spaces. These cells are PAS-positive. In addition, there are lymphoid follicles in alveolar walls along with increased argyrophilic reticulum. Of practical importance, lung biopsy is indicated when the diagnosis is suspected because of the reported favorable prognosis in adrenal corticosteroid-treated patients.

We gratefully acknowledge the assistance of Dr. Oscar S. DePriest III, who performed the lung biopsy, and Christina Carr, who performed the pulmonary function tests.

(*Continued on page 576*)

Hearing Loss in a Child Following Neomycin Irrigation

Report of a Case

PETER A. CAMPANELLI, M.A.*, EVERLINE GRIMES, M.A.†, AND MARC L. WEST, M.D.‡

THE OTOTOXIC PROPERTIES of streptomycin and its salts have been well cited in the medical literature.[1-5] Reports of neomycin ototoxicity, on the other hand, are of more recent origin. This report presents a case of high-tone neurosensory hearing impairment in a child resulting from sinus tract irrigations of the knee-joint with neomycin solution.

Neomycin, an antibiotic produced by a strain of *Streptomyces fradiae* was reported by Waisbren[6] to have the widest antibacterial spectrum of all of the antibiotics. It is primarily bactericidal and effective against the majority of gram-positive and gram-negative bacteria, including virtually all strains of *Staphylococcus aureus*. Topically, it is employed in the treatment of skin and eye infections and as an irrigating solution for the cleansing of traumatic and surgical wounds. In addition, neomycin is administered orally for preoperative cleansing of the intestinal tract. Dawson, McLaren and Sherlock[7] reported its use in the treatment of hepatic coma in which neomycin acts to attenuate ammonia-forming organisms in the intestinal tract.

Because of its toxicity, parenteral use of neomycin is contraindicated except in certain cases of severe and life-threatening infections demonstrating resistance to less toxic antibiotics. Toxic action upon the collecting tubules of the kidney has been reported by Carr et al.[8]

The ototoxic properties of neomycin have been demonstrated by Hawkins and Lurie[9] and Lindsay, Proctor and Work.[10] Electrophysical studies of hearing in the cat by Hawkins and Lurie demonstrated initial degeneration of the external hair cells of the organ of Corti with subsequent degeneration of the inner hair cells. This degeneration was greatest in the basal coil of the cochlea. However, the vestibular system revealed only a slight scattered hair cell loss of the crista. These findings correlate well with the observed clinical effects of neomycin wherein the adult hearing loss appears initially, and to a greater degree in the tonal frequencies above 1,000 cycles per second (c/s).

The results of Lindsay et al, based on histologic study of a human inner ear deafened from parenteral neomycin, were in close agreement with the findings of Hawkins and Lurie in cats. Lindsay and his co-workers revealed absence of the internal hair cells and degeneration of the outer hair cells, pillars, and Deiters' cells. The vestibular epithelium showed no damage. This sparing of the vestibular labyrinth is in agreement with clinical findings that vertigo is not usually a common symptom of toxicity.

Greenwood[11] reviewed the literature and described the clinical and histopathologic ototoxicity of neomycin. In his adult cases the minimum amount of intramuscular neomycin which produced deafness was 8 Gm. administered over a 4-day period. The onset of auditory impairment occurred 10 days after therapy was initiated. In 3 months bilateral neurosensory deafness was complete. The largest amount, reported by Greenwood, was 45 Gm. given over a period of 42 days. The onset of hearing loss was 35 days after therapy was begun, and deafness was complete 4 months after cessation of therapy.

Halpern and Heller[12] reported an adult who received over 600 Gm. of neomycin orally. After 585 Gm. of neomycin had been administered orally the pure-tone audiometric configuration displayed a mild bilateral impairment from 125 through 1,000 c/s. However, the remainder of the tonal responses indicated a precipitous slope above 1,000 c/s. As part of this report Halpern and Heller also recorded a subsequent case of neurosensory deafness in an adult patient who received 6.75 Gm. of neomycin intramuscularly over a period of 7 days. The authors noted that a hearing deficit occurred 7 days after onset of therapy with complete bilateral deafness in 1 month.

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King[13] reported a case of severe deafness in an 18-month-old infant following oral administration of a neomycin compound used in the treatment of enteritis. On audiologic evaluation consistent auditory responses in the sound-field at hearing levels of 80 decibels (db) were recorded. In this case the hearing deficit did not become apparent until at least a week after treatment had ended.

Fields[14] in 1964 reported an adult case of deafness following rectal and colonic irrigations with neomycin solution. The total dosage of neomycin administered was in excess of 960 Gm. over a 2-month period. Fields concluded that the route of drug administration is not always an assurance that toxicity will not result. This caveat is in keeping with the assumptions of Last and Sherlock.[15] They found significant blood levels of neomycin in several instances which were not related to the dosage or duration of therapy.

In addition to King's report of neomycin deafness in a pediatric patient Fuller[16] also observed 2 cases of deafness in children in whom neomycin was administered in aerosol form in the treatment of staphylococcal pulmonary infections sensitive only to neomycin. Although the total dosage was not reported, both children received the medication for a period in excess of 2 years.

The patient whose history is reported here indicates the vagaries of "individual susceptibility" to ototoxic medication.

Report of Case

T.B., a male child, had normal development until 4 years of age. On February 29, 1964 (at the age of 4 years, 7 months) the boy was involved in an automobile accident and suffered a traumatic spinal cord injury at the T6 level resulting in paraplegia. Subsequently he underwent an ileobladder constructive procedure in another hospital. Neurologic examination in March of 1964 revealed no voluntary movements in the lower extremities.

A psychologic examination in October of 1964 (at the age of 5 years, 3 months) produced the following results: Stanford-Binet (L-M) M.A.3-0, IQ 52; Peabody Picture Vocabulary Test (Form B) M.A. 2-5.

The child was fitted with long leg braces with a pelvic band and crutches at this time and began to receive intensive physical and occupational therapy.

A routine evaluation in the Clinical Audiology and Speech Pathology Section was initiated in February of 1965 (at the age of 5 years, 7 months). Speech and language processes were somewhat reduced and in keeping with his obtained mental age. Pure-tone audiometry indicated normal hearing levels bilaterally (10 decibels or better, 1951 ASA reference) for the tonal frequencies 250 through 8,000 c/s.

The child was readmitted as an inpatient to the Crippled Children's Service, Bureau of Maternal and Child Health, D. C. General Hospital, on November 3, 1965 (at the age of 6 years, 4 months) with a diagnosis of draining sinus of the left knee. His admission weight was 56 lbs.

Bacteriological studies of the sinus exudate revealed *Staphylococcus aureus* (coagulase-positive) and paracolon organisms to be present. Cultures for acid-fast and unclassified myobacteria were negative as were studies for fungi. Leukocytes numbered 5,300; the hematocrit was 36 per cent, and the urea nitrogen 18 mg. A urinalysis was normal.

Sterile dressings and saline solutions were prescribed. An X-ray film of the affected area on November 7, 1965 was unremarkable. Beginning on November 16, 1965 50 c.c. of a 10 per cent neomycin irrigating solution was administered every 3 hours by catheter drip into the left knee sinus. The interval was changed to every 6 hours on November 19, 1965 and discontinued on November 24, 1965. Temperature, pulse and respiration were within normal limits during this period.

The initial baseline audiogram, it is recalled, was done in March 1965 and revealed normal auditory acuity bilaterally. Monitoring pure-tone audiometry begun 7 days after initiation of neomycin therapy revealed normal hearing (10 db or better, 1951 ASA reference) up to and including 2,000 c/s bilaterally. Depressed acuity was noted at the tonal frequencies of 4,000 c/s (30 db), 6,000 c/s (70 db), and 8,000 c/s (60 db) for air-conducted signals. Equal depression at 4,000 c/s for bone conduction suggested a high-tone neurosensory hearing impairment. Tympanic membranes were examined and found to be normal, suggesting a cochlear or transcochlear deficit.

Neomycin medication was discontinued on November 24. The next day the audiometric picture remained generally unchanged save for further depression in the right ear at 4,000 c/s from 30 db to 45 db hearing levels. Speech audiometry administered on November 26 revealed normal acuity levels (10 db or better) bilaterally for verbal material (speech reception threshold) as well as normal discrimination ability (100 per cent) for phonetically balanced word lists.

Daily monitoring audiometry was conducted from November 23 to December 15, at which time it was done every other day. No auditory threshold shifts were noted (except on November 25, as stated above) when compared to the initial evaluation made during the period of medication.

After 1 month following termination of neomycin medication (December 22) the pure-tone, speech reception, and speech discrimination levels had not changed. Also, on this date tone-decay tests were administered to clarify the site of lesion in the auditory nervous system. Mild tonal decay was noted at 4,000, 6,000, and 8,000 c/s bilaterally, suggesting further evidence for cochlear involvement. This is in keeping with the findings of Hawkins and Lurie in the cat and of Lindsay et al in the adult human ear.

Auditory evaluation on December 30 indicated no change. Audiologic assessments were done on March 29, 1966 and June 3, 1966, 4 and 6 months, respectively, after discontinuation of neomycin therapy. Threshold hearing levels were unchanged, indicating a permanent, bilateral, high-tone neurosensory impairment. Fortunately, social adequacy for the acuity and understanding of speech through the ear was not impaired.

Discussion

Our clinical experience with this case allows us to make several observations. Some of these have been stated previously elsewhere, but we believe they bear repeating.

Individual susceptibility to ototoxic medication should always be considered, even though dosages are administered which are considered to be at or below reported tolerance levels.

Route-of-drug administration can be considered a variable but only in the case of the individual undergoing therapy. Our patient theoretically might have experienced a greater degree of hearing impairment had the drug been administered in a different fashion. The use of an irrigating solution may have been fortunate in that it resulted in minimal depression of hearing for this child.

Whenever ototoxic medication, whether actual or suspected, is employed, monitoring pure-tone audiometry should be a complementary adjunct. Although conditions did not permit the initiation of immediate premedication audiometry, such a procedure is deemed essential as a baseline reference to compare any changes which might occur. A precise check on the condition of the auditory nervous system is provided by pure-tone audiometry administered over time and continued after cessation of therapy.

In the event that depressed auditory acuity occurs during or after drug therapy a complete audiologic assessment is helpful in measuring related parameters of the auditory system.

Attention should be directed to the fact that neomycin, when used in an irrigating solution, may cause hearing impairment. We were unable to find published references relating to the audiotoxicity of neomycin when used as an irrigating solution in joint cavities.

The authors express their appreciation to Gertrude L. Bramley, M.D. and John P. Adams, M.D. for their helpful comments in the preparation of this paper.

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PRESIDENT'S PAGE

THE DANGER OF DISPUTES

When abrupt social changes such as we are now experiencing take place it is inevitable that the resulting dislocations will lead to disagreements and disputes. In view of the profound effect of Federal legislation on the economics of medical care, controversy in this area is particularly prone to occur. Fortunately, in all but the exceptional case the problem is resolved promptly by reasonable and thoughtful negotiation.

The current controversy between Group Hospitalization, Inc. and the Washington Hospital Council would seem to be the exception. What appears to be an unyielding and rigid attitude on the part of some of the involved parties has led to a breakdown in negotiations. Unfortunately, the publicity given to this dispute over contracts in the local news media has done little to settle the disagreement or to improve the public image of medicine.

The Medical Society of the District of Columbia and its officers have been deeply concerned and disturbed over this apparent impasse; this concern relates directly to the fact that it is the medical care of the public rendered by members of our Society that is most critically involved. The Executive Board of the Medical Society has taken vigorous steps to bring about a conciliation through communications with the Washington Hospital Council, all hospital administrators in the area, and officials of Group Hospitalization, Inc. It had appeared that our efforts were to be rewarded inasmuch as agreement seemed imminent a short time ago. However, negotiations again broke down, as a result of which termination of contracts between many hospitals and Group Hospitalization, Inc. is again threatened. The net effect of this would be that subscribers would have only 80 per cent of their hospital bills paid by Group Hospitalization.

If this controversy is not terminated in the near future, the Executive Board of the Medical Society plans to renew its efforts towards conciliation in a more energetic and demanding manner.

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5-8 years . . .	8 mg.	1 tsp. 4 times daily
8-12 years .	10 mg.	1 tsp. 5 times daily

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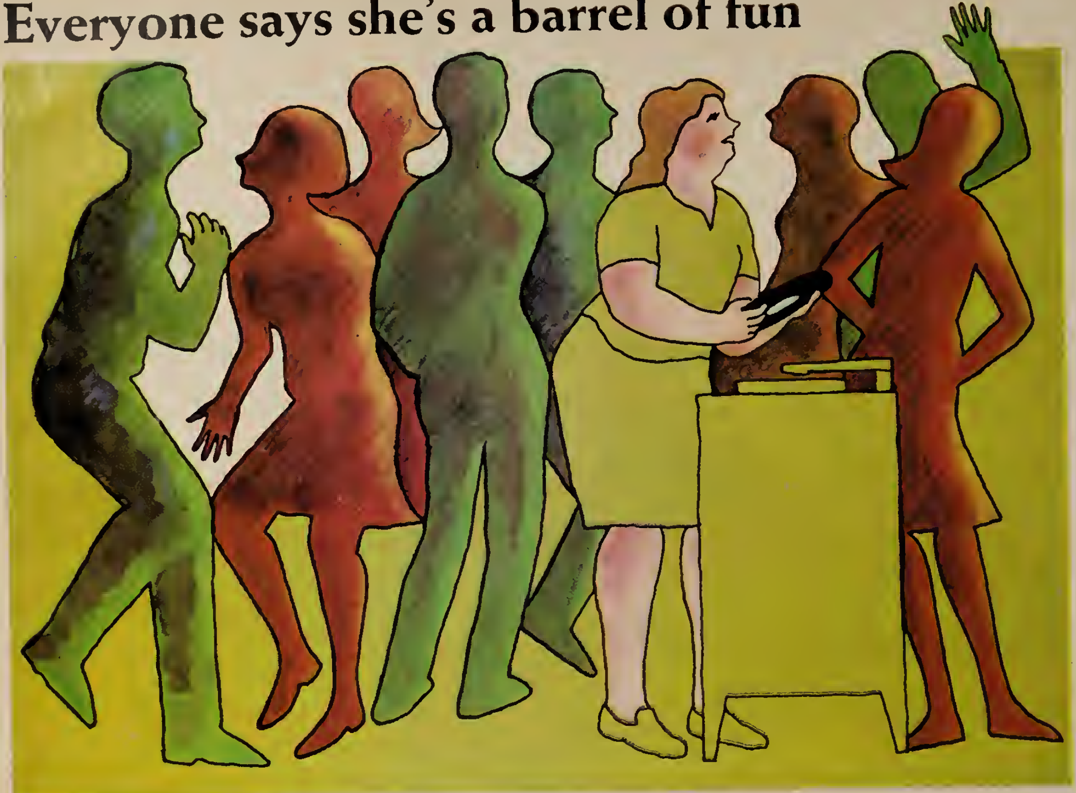

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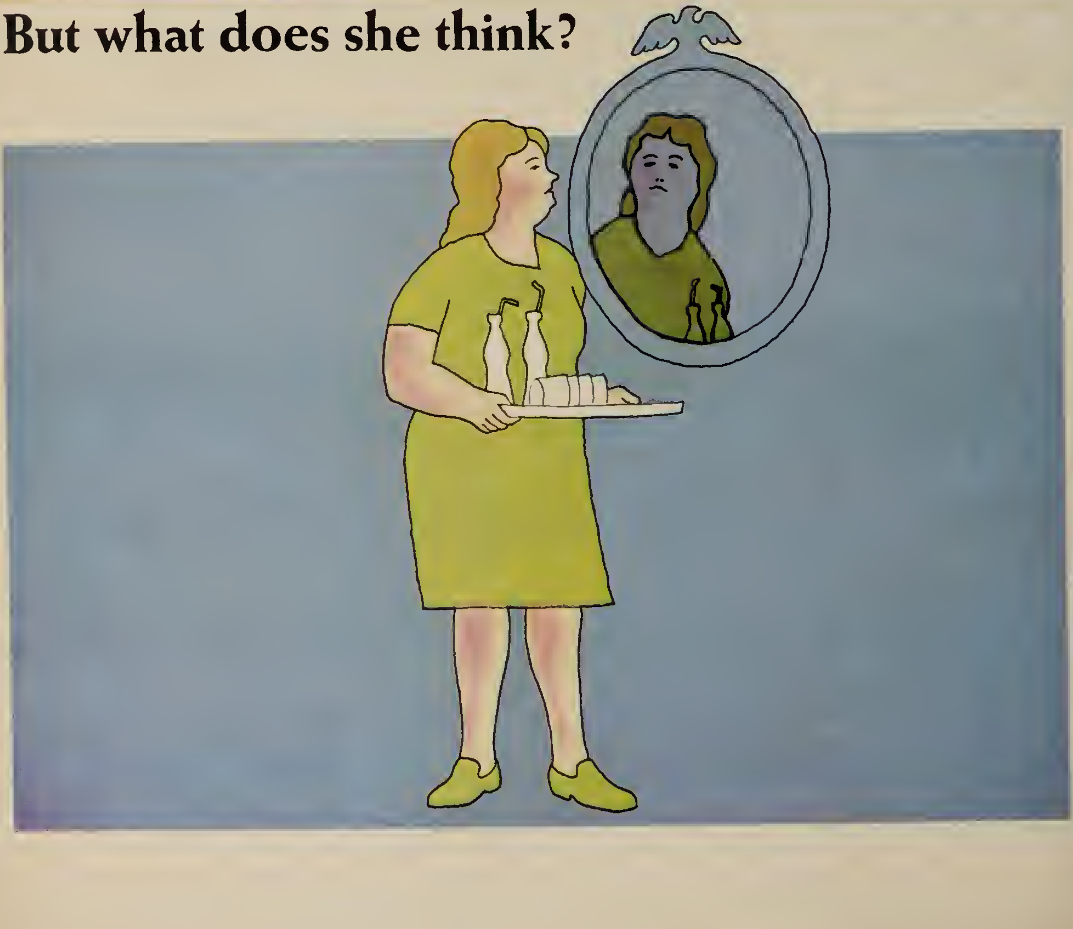

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Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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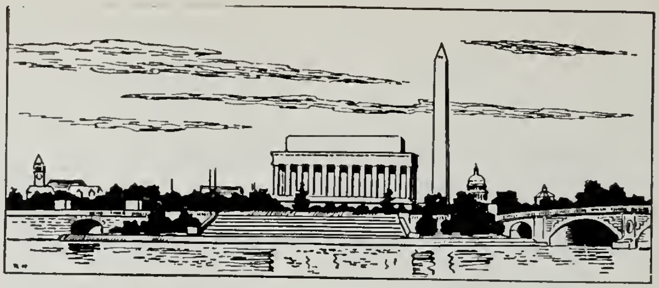

EDITORIALS

The 60th Annual Southern Medical Association Meeting

The Medical Society of the District of Columbia will be host to the Southern Medical Association in this city, November 14 to 17, 1966. The Society is thus sharing its Annual Assembly on the occasion of the Sixtieth Annual Meeting of "The Southern." The last occasion of this joint effort was S. M. A.'s Fiftieth Anniversary, when the organization's members were welcomed by Dr. W. Ross Morris, then President of the Medical Society of the District of Columbia.

It is appropriate that for the coming meeting the District is represented by another distinguished surgeon and teacher, Dr. Robert J. Coffey. This is appropriate, because through the years "The Southern" has directed its efforts at continuing medical education, and as the Nation's second largest medical association it has remained nonpolitical.

Each of its 22 Specialty Sections are presenting up-to-date information on subjects of general interest. Many of some 300 papers to be presented will be contributed by Washington physicians. Several joint symposia are planned, including one shared by the gastroenterologists and pathologists on recent advances in malabsorptive diseases. Scientific and technical exhibits will be included, as well as programs over color television. Surgical operations will be broadcast "live" from Doctors Hospital.

Organizations meeting conjointly with S. M. A. are the Southern Chapter of The American College of Chest Physicians, The College of American Pathologists, The Flying Physicians' Association, The Radiological Society of North America, and The Southern Gynecological and Obstetrical Society. In addition "The Southern" will serve as host to 2 senior medical students from each of the schools in its geographic area, and also will award Residency Training Grants to doctors in training at many of the area's medical centers.

A number of social functions are planned. The President's Luncheon on Tuesday, the 14th of November will be of general interest because the honored speaker will be Milford O. Rouse, M.D., President-elect of the American Medical Association. The Women's Auxiliary will also meet with the wives of the District of Columbia physicians.

There will be no registration fees. The registration desk will be in the lower lobby of the Washington Hilton. It is with great pleasure that all physicians are invited to attend this meeting.

George P. Blundell, M.D.
Councilor for the District of Columbia,
The Southern Medical Association

The Impact of Medicare on D. C. Nursing and Personal Care Homes

With the advent of Medicare and the incorporation of the nursing home portion of the Medicare legislation in January 1967, there is an understandable increasing concern about the status of the nursing and personal care homes of the District of Columbia. The deficiencies of these homes are well known and range from inadequate medical care to poor food to absence of recreational and rehabilitation programs. It is assumed that many of the present homes will be unable to meet the probable and desirable upgraded standards in the process of establishment through Medicare.

Opinions expressed in contributions to the Editorial Section are those of the writers and do not necessarily reflect the views of the Medical Society of the District of Columbia

The Committee on Geriatrics of the Washington Psychiatric Society is of the strong and unanimous opinion that planning and action now will help insure realistic and appropriate standards of care. It considers this period an excellent opportunity for the introduction of active care in the nursing and personal care homes. It is the opinion of this Committee that the rehabilitation specialties and psychiatry should participate actively in nursing home care. A very high percentage (estimates range from 50 to 80 per cent) of nursing home residents suffer significant measures of mental dysfunction including depression and functional disturbances as well as organic impairments.

The Committee made certain recommendations to the Commissioners of the District of Columbia and the D. C. Department of Public Health. Among them were the following:

1. All nursing and personal care homes as well as old-age residential hotels, eleemosynary and proprietary, be placed under the direct and primary supervision of the D. C. Department of Public Health; that the Department of Public Health establish, with advice and continuing counsel, improved standards of care comparable to those existent in other states and to those promoted by national organizations that have long been concerned with nursing homes. Licensure should depend upon institutions meeting these standards. The present multiple regulation involving 5 agencies has the unfortunate consequence of insufficient if not conflictual or indifferent regulation. As of 1963, 39 states and territories had given to their health departments licensure responsibility.

2. The D. C. Welfare Department rates for indigent care in care homes be made realistic and thereby enhance the possibility of nursing homes improving the care offered. From national data, minimal nursing home care requires \$10/day or \$300/month, nearly 3 times the amount presently available for the indigent aged in the District.

3. Specialists in rehabilitation, gerontology and psychiatry collaborate with other specialties in both the establishment of standards of care and inpatient care. Rehabilitation and psychiatric treatment are provided for under Medicare.

4. A Select Committee or planning group be formed with broad representation of all organizations involved, or which should be involved, in nursing home care. Providers, consumers, financiers, regulators, etc. should be represented or consulted. It is strongly advised that every effort be made for the direct participation of older people themselves on this Committee.

The Select Committee would have among its specific purposes the review of national and local conditions in care homes, the establishment of standards for such homes in the District, and the continuing review of the situation during the first years of the Medicare program to facilitate revision as a reflection of experience.

The Report and Recommendations of the Committee on Geriatrics were not offered as representing "the solution" to the manifold issues involved in the District nursing-home situation. This fact in itself reinforces the need for the Select Committee which was recommended to include the wide range of specialists who could work toward more comprehensive "solutions."

We hope that planning may precede Medicare rather than have chaos follow its inception.

Robert N. Butler, M.D.
Chairman, Committee on Geriatrics,
The Washington Psychiatric Society

Design for Increasing Attendance at Medical Meetings

Attendance at meetings of the many small medical societies in this overorganized area is, undoubtedly, a continuous and vexing problem. How to meet the problem faces new officers as they begin their fall programs. Of interest is the following letter, somewhat abridged, whereby President William G. Ballinger of the D. C. Dermatological Society hopes to stimulate reluctant members to attend and participate in meetings:

"During the past year the attendance at our meetings has been characterized by either a complete or, at least, frequent absence of many of the stalwarts of our organization. The 'faithful' would like them to join us this coming year.

"My own feeling is that our meetings serve 2 purposes. One is the opportunity to present problem cases from our practices for help with the diagnosis or therapy. Some object to cases being improperly worked up and prefer to exclude these, and this is the prerogative of the man in charge of the meeting. To me this has the potential for discouraging members from bringing their problems for help, and I would hope that most institutions hosting our meetings will make allowance in their programs for last minute cases.

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"The other purpose is to educate ourselves through the presentation of 'museum piece' cases, well worked-up unusual diseases, and short talks by our members and outside speakers. While the latter is more educational, it also permits the audience to relax and offers none of the give-and-take that the 'Case for Diagnosis' presents. It is discouraging for the presenter to hear few or no comments regarding diagnosis or therapy when discussion is opened, and I hope to alleviate this by calling on our experienced dermatologists for help, whether they volunteer to speak or not.

"I plan to open the discussion portion of the meeting promptly and to finish promptly. If it seems that there are too many cases to discuss adequately in the time allotted, those that are problems and those with pre-assigned discussants will be given priority.

"To encourage attendance, every effort will be made to close our meetings by 10:00 p.m. Another possibility is to have our meetings begin at 6:00 p.m. with the patient presentation and discussion first, followed by dinner at 8:00 or 8:30. This is done quite successfully in San Francisco, but they have a central location, Letterman Hospital, for their meetings. If the meetings are held in the same location each time it means that hospitalized patients have to be transported by ambulance or car, a strong disadvantage in our spread-out metropolitan area. Perhaps many of you would prefer an earlier meeting without dinner. Please communicate with me and make your desires known. Your officers want to follow your wishes."

If other societies or sections have found ways to attract both old and new members, your editorial staff will be glad to hear from them and to pass on any worthwhile suggestions. It is also hoped that the dermatologists will report in the spring how successful attendance at their 1966–67 meetings proved to be.

A. L. E.

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Report on Finances and Administrative Services of Medical Service*

Since its inception Medical Service of the District of Columbia has enjoyed a remarkable growth, not only in the number of subscribers who contribute funds for the payment of physicians' services but in the variety of physicians' services for which payment is made. The year 1965 was no exception. It is significant that in 1965 Medical Service paid $7,900,000 more for physicians' services than was paid in 1964. The total of $35,142,000 paid for physicians' services in 1965 would provide more than $11,000 for each physician participating in Medical Service.

While Medical Service was paying out record amounts for physicians' services in 1965, subscription income did not keep pace with increased benefits and greater utilization, and the Medical Service reserve was diminished by $737,283, leaving a total reserve at the end of the year of $5,983,141. This reserve would provide payments for 1.91 months of claims and operating expense, somewhat less than the reserve position recommended for Blue Shield Plans by the National Association. Thus, steps were taken in September 1965 to increase subscription charges sufficiently to assure that income will exceed expense during the current year.

For your information, I should like to take this opportunity to summarize the balance sheet of Medical Service as it compares the year 1964 with 1965.

	Year 1964	Year 1965	Increase
Total Assets	$17,017,183.72	$19,403,050.84	$2,385,867.12
Total Liabilities	10,296,758.83	13,419,909.50	3,123,150.67
Reserve for Medical Service	6,720,424.89	5,983,141.34	(737,283.55)
Total Liabilities and Reserves	$17,017,183.72	$19,403,050.84	$2,385,867.12

Our comparative operating statements for 1964 and 1965 are as follows:

	Year 1964	Year 1965	Increase
Income:			
Earned Subscription Charges	$29,854,500.89	$36,861,169.53	$7,006,668.64
Income from Investments	317,599.14	350,176.67	32,577.53
Total Income	$30,172,100.03	$37,211,346.20	$7,039,246.17
Expenses:			
Claims	$27,195,783.86	$35,142,027.25	$7,946,243.39
Operating Expense	2,104,659.07	2,454,899.38	350,240.31
Total Expense	$29,300,442.93	$37,596,926.63	$8,296,483.70
Total Reserve Addition	$880,213.54	$(737,283.55)	$(1,617,497.09)

Enrollment increased in 1965 by 25,525 participants. At the close of the year there were 1,052,897 persons covered by Medical Service, of which 537,161 were enrolled in the Federal Employee Program. In a report presented by the Enrollment Committee of the National Association of Blue Shield Plans, Medical Service is fourteenth in the total number of persons enrolled, eighth in the percentage of population enrolled, and first in the number and percentage of subscribers enrolled in the Federal Employee Program. It is gratifying to find that Federal employees in the Washington area, as well as Nationwide, continue to choose the Blue Cross-Blue Shield Program over all other available programs combined.

With approximately half a million participants covered under the Supplemental Benefits portion of the Federal Employee Program, and more than 160,000 persons covered under our local Comprehensive Contracts, we find that about 63 per cent of all participants are protected under Major Medical or Supplemental benefits. Payment of physicians' services under this type of coverage has increased tremendously the amount paid to local physicians for services and charges which are not covered under the subscriber's Basic Contract.

The experience gained by Medical Service in providing payment based upon reasonable charges under these contracts will enable Medical Service to better carry out its role as carrier for the medical insurance portion of Medicare which will affect some 140,000 aged persons in the Washington Metropolitan Area.

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* Presented at the Annual Meeting of Participating Physicians of Medical Service of the District of Columbia, May 25, 1966.

As Medical Service grows, so does the administrative force, and as new programs are instituted by Medical Service, so are new departments established to administer them. When Medicare becomes a reality on July 1, 1966 Medical Service will have a Medicare Department which for the past several months has been developing procedures for the administration of the Medicare Program and coördination of activities with the Basic Medical Service Claims Department.

Despite the increased enrollment in contracts offering a wider variety of services and a consequent increase in claims activity, the operating cost for Medical Service in 1965 amounted to 6.6 per cent of earned subscription income, down from 7 per cent in 1964 and substantially below the national average of 8.44 per cent. Other comparisons with national averages show that our reserves, which are equivalent to approximately 2 months of claims and operating expense, are, at present, below the national average of 3.3 months of claims and operating expense. In making payment for physicians' services, Medical Service used 95 per cent of subscription income as compared with the average for all Blue Shield Plans of 90 per cent.

Under an operating agreement between Group Hospitalization, Inc. and Medical Service of D. C., GHI acts as the agent of Medical Service in such administrative functions as the enrollment of subscribers, billing and collecting subscription payments, and the payment of claims. Despite the use of modern electronic procedures for storage of information, statistical development and claims processing procedures, more and more space, equipment and personnel are needed to keep up with the ever-growing work load. In 1965 the Basic Claims Department processed some 814,631 Medical Service claims, a record of more than 3,100 each working day. The Claims Department is composed of 121 employees, 18 of whom are Registered Nurses engaged in a variety of activities such as coding claims' information for statistical and payment purposes, determining eligibility, assigning fees, and answering inquiries. A recent check shows that Claims Service personnel alone receive 588 telephone calls a day. A similar variety and volume of activity take place in other departments, and while some errors may be made and some delays may occur, the great bulk of the work is performed promptly and efficiently.

The growth of Medical Service in enrollment and the expansion of physicians' services covered have been accompanied by a continuing increase in the numbers of physicians participating in the program. During 1965 there was a net increase of 126 physicians participating in Medical Service, bringing the total to 3,097. The continuing participation and support of physicians in the Washington area are essential to the functioning of Medical Service as a Blue Shield service benefit plan. As we look ahead to fulfilling our role as the carrier for Medicare in the Washington area, we will continue to administer responsibly the many other programs with which we are engaged at present, and I am confident that with the continued coöperation of Participating Physicians, Medical Service of D. C. will serve the interests of physicians and the public alike in an even greater degree than in the past.

George B. McGovern
Executive Vice President

Film and Self-rating Scale on Measurement of Depression

"The Measurement of Depression" is a film depicting the development, validations, and use of a scale for the quantitative measurement of depression. The film is designed for medical educational purposes at meetings of hospital staffs, county societies or specialty groups. The self-rating scales, available in quantity for use in office practice, come complete with full instructions.

The scale consists of a list of 20 statements expressed in the common language of the patient. The statements comprehensively delineate widely recognized symptoms of depression including disturbances of mood, biological and psychological function. Testing and scoring patients usually requires less than 5 minutes. Originally devised by Dr. William W. K. Zung, a psychiatrist of Durham, N. C., for use in psychiatric research, the scale readily lends itself to the general practice of medicine where most depressions are first encountered.

Use of the scale in a variety of patients with physical complaints without apparent organic basis may uncover and measure depression in so-called "hidden depressions," saving valuable time in the clinic and several sessions of probing interviews.

Both the film and pads of the self-rating scale are available free upon request from Medical Film Department, Lakeside Laboratories, Inc., 1707 East North Avenue, Milwaukee, Wisconsin 53201.

Medical Services International[*]

Medical Services International, Inc., with headquarters in Washington at 1712 Eye Street, N.W., is one of the newer charitable foundations to enter the field of international medical assistance. Although it has been in existence only since March of 1964, MSI already has 3 physicians and a nurse assisting in the health programs of Kenya and Tanzania.

The organization has established an MSI Scholarship in Medicine at Howard University. The first-year recipient is Mr. Amadur Barrie, a native of Sierra Leone, who was recommended by Robert Jason, M.D., former Dean of the Medical School.

MSI was also the prime mover in building up the medical library of the Lovanium University, Leopoldville, Republic of the Congo. Lovanium, with a fairly large body of medical students, had only about 100 usable reference texts in its entire medical library until MSI approached the publishers of medical texts and persuaded them to donate a large quantity of books. Shipment to Leopoldville was arranged through the International Exchange Office of the Smithsonian Institution.

Frederic D. Chapman, M.D., a long-time member of the D.C. Medical Society, assumed the presidency of MSI on January 1, 1966.

"It may seem strange," Dr Chapman says, "that we operate a charitable organization which doesn't believe in charity per se. By that I mean we don't believe in outright giving, but we are prepared to assist those countries that are making a sincere effort to improve their health programs through their own resources.

"We know from our negotiations with many of the newer African countries that the salary scales they have established for physicians, particularly American physicians, are very liberal. In some cases we have heard of physicians whose salaries exceed those of the cabinet ministers of the country. The trouble arises, of course, when we translate these otherwise munificent salaries into American dollars."

In summing up the philosophy under which MSI operates, Dr. Chapman stated: "Our purpose, and in fact, the major reason we are in business is to find professionally qualified physicians who are willing to enter into contracts of employment with these newer countries. We then provide grants or subsidies to those physicians whose financial status just does not permit them to accept the going rate the country can offer.

"We feel strongly that we have 3 grave obligations inherent in our assistance programs. The first is to the government of the host country itself, because we want to be assured that we recommend only well qualified, well motivated physicians with stable personalities who will be assets in these positions. The second is to the physician himself, because we want to place him in a very challenging situation which will extend his professional capabilities; but we also want him to be able to maintain a reasonable standard of living and to meet fixed financial obligations, such as college tuition for his children. The third, and to our minds equally as important, is our obligation to our contributors to see that their money is invested wisely, not just given away. So you see, in this sense, we really don't believe in charity."

The Board of Directors of MSI includes A. L. Severson, Sunnen Foundation, St. Louis, Missouri; Samuel R. Milbank, Milbank Memorial Fund, New York; W. Furness Thompson, Smith Kline and French Foundation, Philadelphia; Charles E. Saltzman, Goldman, Sachs and Company, New York; and Henry Sears, Henry Sears and Company, New York. Dr. Leroy E. Burney, former Surgeon General of the Public Health Service, was recently appointed Chairman of the Board of Medical Advisors

MSI has both Federal and D. C. tax-exempt status and, in addition, is registered in the District of Columbia and in New York as an organization authorized to solicit contributions. Contributors thus are assured that contributions are tax-deductible.

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[*] Editor's note: An increasing number of groups are now offering medical assistance to foreign countries. In order to keep our members informed of their current activities and needs, we are planning to publish a series of articles submitted by such groups, of which this is the first.

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Health Dept. Notes

The Aged and Elderly

The "Aged and Elderly" population of the United States is known to be increasing every year. With this increase goes the need for new and different kinds of medical care and additional treatment facilities. Some of this need is reflected in the demand for more nursing homes and beds for the older, chronically-ill patient whose continuing care does not require the intensive level of service available in the acute general or specialty hospital. Medicare benefits available to these patients are certain to make this demand even greater in the immediate future.

But many of the elderly ill need only occasional medical attention, usually in periods of stress or crisis. This may perhaps lead to brief hospitalization. What they require much of the time is access to a private physician or a public health clinic. Here they can receive medical counseling, treatment and medication on an outpatient basis, and return to their homes until another such visit is indicated.

The Health Department has established this type of clinic in the Arthur Capper public housing project in Southeast Washington. This is staffed full-time and is available to the more than 500 elderly residents of the Arthur Capper project. There is also a part-time clinic operated by the Health Department in the Garfield Terrace housing project for use by the elderly living there.

There are numerous reasons why these housing projects require such a clinic placed within them. The income for housing residents, especially the older, retired, no longer productive resident, is unbelievably low. Many of these persons have less than $100 to live on each month. It is income pieced together from welfare benefits, perhaps Social Security, and other limited sources. These residents cannot afford to travel by cab or bus, even occasionally, to reach a clinic across town.

Many of them are also too infirm to attempt such travel. They often have debilitating conditions, are poorly nourished, have difficulty walking, and are often crippled by arthritis. The clinic must obviously be where they are if they are to be able to use it.

The clinic intended for the older person must also reflect his actual needs. Experience at Arthur Capper has shown that these include assistance in diet planning, food purchasing, and nutrition; recreational therapy in a somewhat social setting; direct patient care and treatment of medical problems; and medical counseling and advice on a wide range of patient-centered problems.

To accomplish this the Arthur Capper public housing clinic has a physician, public health nurse, medical social worker, dietitian, and clerk-receptionist. This staff has been attempting to deal with many different kinds of health or health-related situations which have been presented to them.

The conditions seen most often are, predictably, heart and circulatory disease, diabetes, arthritis, obesity, dental difficulties, some tuberculosis, mental confusion and depression in the very old, and similar chronic illnesses. If other than outpatient care is required, the resident is referred to an appropriate specialty service or to a public hospital.

The Arthur Capper Clinic began operation more than a year ago. It has been renovated while in use and changes have been made in its physical organization to permit better service to the patients. Both the Arthur Capper and Garfield Terrace clinics can be prototypes for other such facilities for outpatient care of the elderly impoverished living in the District of Columbia.

Murray Grant, M.D., D.P.H.
D. C. Director of Public Health

Influenza Vaccine 1966-1967

Recommendations of the Committee on Communicable Diseases

The composition of the 1966–67 vaccine is the same as that prepared for 1965–66. This is due to the fact that there has been no significant variation in the influenza viruses to merit a change in the vaccine this year. Influenza was reported in 49 of the 50 states during the winter and spring of 1965–66. Type A2 virus was most prevalent in the western states and type B predominately east of the Mississippi River. School absenteeism was for the most part due to type B influenza.

While annual influenza vaccine may not be indicated for all individuals, it should be given to persons in groups which are known to experience high risk. Such groups include persons of all ages who suffer from chronic debilitating disease, e.g., chronic and cardiovascular, pulmonary, renal or metabolic disorders, and in particular:

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1. Patients with rheumatic heart disease, especially those with mitral stenosis.

2. Patients with other cardiovascular disorders, such as arteriosclerotic heart disease and hypertension, especially those with evidence of frank or incipient cardiac insufficiency.

3. Patients with chronic bronchopulmonary diseases, as, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, and pulmonary tuberculosis.

4. Patients with diabetes mellitus and Addison's disease.

Patients residing in nursing homes, chronic disease hospitals, and other such environments should be considered as particular risks since their more crowded living arrangements may allow greater spread of disease once an outbreak has been established.

Those working with sick people or with transients are essentially a high risk group and should have an influenza immunization.

Time of vaccination. Vaccination should begin as soon as practicable after September 1 and ideally should be completed by mid-December. It is important that immunization be carried out before influenza occurs in the immediate area since there is a 2-week interval before the development of antibodies.

Dosage and Schedule

Primary immunization. Individuals not vaccinated since July 1963, when the last major change in vaccine formulation was made, should receive an initial subcutaneous dose of polyvalent vaccine followed by a second dose 2 months later. It is to be pointed out, however, that even a single dose can afford significant protection. A second dose given as early as 2 weeks following the first will also enhance the protection.

Adults and children over 10 years, 1.0 ml. subcutaneously on 2 occasions as specified above.

Children 6 to 10 years, 0.5 ml. subcutaneously on 2 occasions as specified above.

Children 3 months through 5 years, 0.1–0.2 ml. of vaccine given subcutaneously on 2 occasions, separated by 1 to 2 weeks, followed by a third dose of 0.1–0.2 ml. about 2 months later.

Since febrile reactions are common following influenza vaccination, an antipyretic may be indicated.

Booster immunization. Individuals vaccinated since July 1963 need receive only a single booster of vaccine at the dose level specified for the primary series. For those in the older age-groups who have previously experienced undue reactions to influenza vaccine, a re-vaccination dose of 0.1 ml. given by a careful intracutaneous injection can be expected to give an antibody response which is somewhat comparable to that induced by the 1.0 ml. subcutaneous dose. The intracutaneous route is not recommended, however, for use in other than these special cases.

Contraindications. Since the vaccine viruses are produced in eggs, the vaccine should not be administered to those who are hypersensitive to eggs or egg products.

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Policy Statement on Air Pollution*

THE NATION'S CAPITAL has had an increasing air pollution problem, first well defined in the last decade. As our population—and our automobiles—increase in numbers, an increasing amount of fuel is consumed which burdens our not unlimited blanket of air with combustion gases. It has been estimated that in 1 average day in this Metropolitan Area we burn 1½ million gallons of gasoline, 6,000 tons of coal, 200 million cubic feet of natural gas, and over 1 million gallons of fuel oil. Heavy coal consumption even occurs in the summer months because this fuel is used to produce electricity. In addition we burn 2,400 tons of trash and unmeasured quantities of construction refuse and leaves. Both fuel burning and other activities produce huge quantities of combustion products, smoke and particulate dust.

Our air has been continuously monitored since January, 1962 by the D. C. Department of Health in coöperation with the U. S. Public Health Service. At times we have relatively high levels of sulfur dioxide which with moisture has formed acid in the air and even dissolved stockings on pedestrians. Recently our "photochemical" smog has been found at concentrations which produce eye irritation, vegetation damage, and visibility reduction on 30 days of a year. Numerous studies have been made which indicate that human health is adversely affected by the kind of air pollution we now have. Pollutants irritate skin, eyes, nose, throat and lungs. Exposure to relatively low levels of urban air pollution over months to years predisposes people—even those who don't smoke—to chronic bronchitis, emphysema, lung cancer, pneumonia, and chronic heart disease. Susceptibility to virus infections is increased in areas where air pollution is high.

In addition to ill health resulting from chronic cumulative pollution there is a threat that a combination of weather conditions will allow the pollutants to stagnate and become highly toxic so that this city may experience an acute epidemic of smog poisoning with fatalities such as have occurred in other cities. For these reasons the D. C. Medical Society regards air pollution in the District of Columbia as a matter of urgent public health importance. Our public health agencies must broaden their studies and channel more funds to the pursuit of adequate measures to control the above problems.

Blowby devices, costing about $20.00, should be mandatory for all cars registered in the District within a year. Within 2 or 3 years all cars should be forced to meet standards based on maximal permissible exhaust emissions. Funds have already been allocated for a modern incinerator to replace the open-burning Kenilworth dump which handles one-fourth of the city's trash. This should be built without further delay. Other measures will be needed also, aimed at preventing pollutants from entering the air. This should be done preferably as part of a coördinated effort by the Metropolitan Washington Council of Governments.

A laissez-faire attitude toward air pollution is not compatible with the basic need of our population to breathe comfortably and safely. We must be willing to accept the costs and disciplines involved in applying available technical control measures to reduce pollution well below present levels. Time is important because the problem is worsening as population grows. Clean air must be restored.

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* Prepared by the Committee on Environmental Health and adopted by the Executive Board of the Medical Society of the District of Columbia, July 25, 1966.

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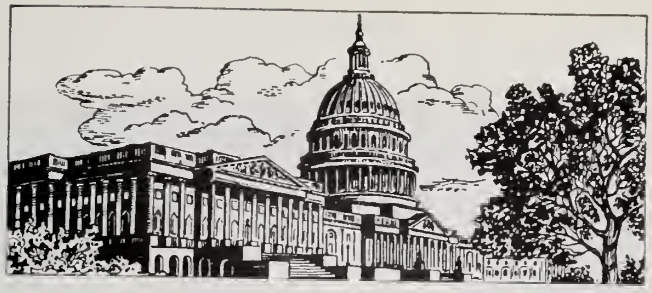

NEWS & PERSONALS

Summary of Executive Board Actions

Proceedings of July 25 Meeting

Dinner for the Executive Board members was served at 6:30 p.m. in the Exhibit Hall of the Medical Society of the District of Columbia, July 25, 1966. Dr. J. Spencer Dryden, Chairman, presided over the meeting. Present were Drs. C. Willard Camalier, Jr., Robert J. Coffey, Karl C. Corley, Henry D. Ecker, Claudine M. Gay, Raymond T. Holden, Edward W. Nicklas, Lawrence A. Rapee, Paul R. Wilner, and Mr. George W. Cooley, Secretary. Also present was Dr. J. Rogers Young, Chairman of the Committee on Occupational Health. The meeting was called to order at 7:15 p.m.

The minutes of the meeting of May 23, which had been mailed previously, were approved.

Committee Meetings: The following committee meetings were reported by the Secretary as having been held since the Board last met:

May 24	Liaison Committee with Medical Schools and Hospitals
25	Committee on Extended Care and Home Care
25	Committee on Child Welfare
26	Committee on Smoking and Health
26	Traffic Committee
27	Committee on Medicolegal Problems
31	Committee on Medical Ethics and Professional Conduct
June 1	Committee on Blood Banks
6	Insurance Committee
7	Relative Value Study Committee
14	Committee on Hospital Utilization
15	Board of Credentials
16	Committee on Occupational Health
16	Committee on Environmental Health
21	Committee on Public Information and Education
22	Committee on Child Welfare
23	Cancer Study Committee
30	Committee on Smoking and Health
July 6	Fee Review Committee
13	Committee on Blood Banks
13	Board of Credentials
14	Ad Hoc Committee on Hospital Regulations
19	Grievance Committee
19	Special Membership Meeting
21	Committee on Extended Care and Home Care
21	Traffic Committee

Board of Credentials: On recommendation of the Board of Credentials, the following applicants for membership and changes in membership status were approved:

Active Members

Joseph Berkenbilt, 2121 Pennsylvania Avenue, N.W.
David Corn, 1835 Eye Street, N.W.
Idus J. Daniel, Sr., St. Elizabeths Hospital
Don T. Mosher, Veterans Administration Hospital
Sophie L. Perry, D. C. General Hospital
Harry C. Press, Jr., Freedmen's Hospital

Associate Members

Nicholas H. Maganias, Veterans Administration Hospital
Lewis Antoine Ottenritter, 8218 Wisconsin Avenue, Bethesda, Md.
Anne Zevallos, Greenbelt Professional Building, Greenbelt, Md.

Transfers

Active to Life: Henry L. Darner
Active to Associate: Walter Atkinson, Joseph F. Schanno, and Reuben Sorkin
Associate to Special: David O. Smith
Resident-Intern to Active: Horace G. Ward, Jr.
Resident-Intern to Associate: Charles P. Waite

*Resignations**

Associate: William Cody, Leo M. Curtis, Bruce L. Gilmore, Ross M. Lehman, Jr., Jose Navarrete, Richard H. Pollen, Pauline A. Swarm, and S. Ross Taggart.

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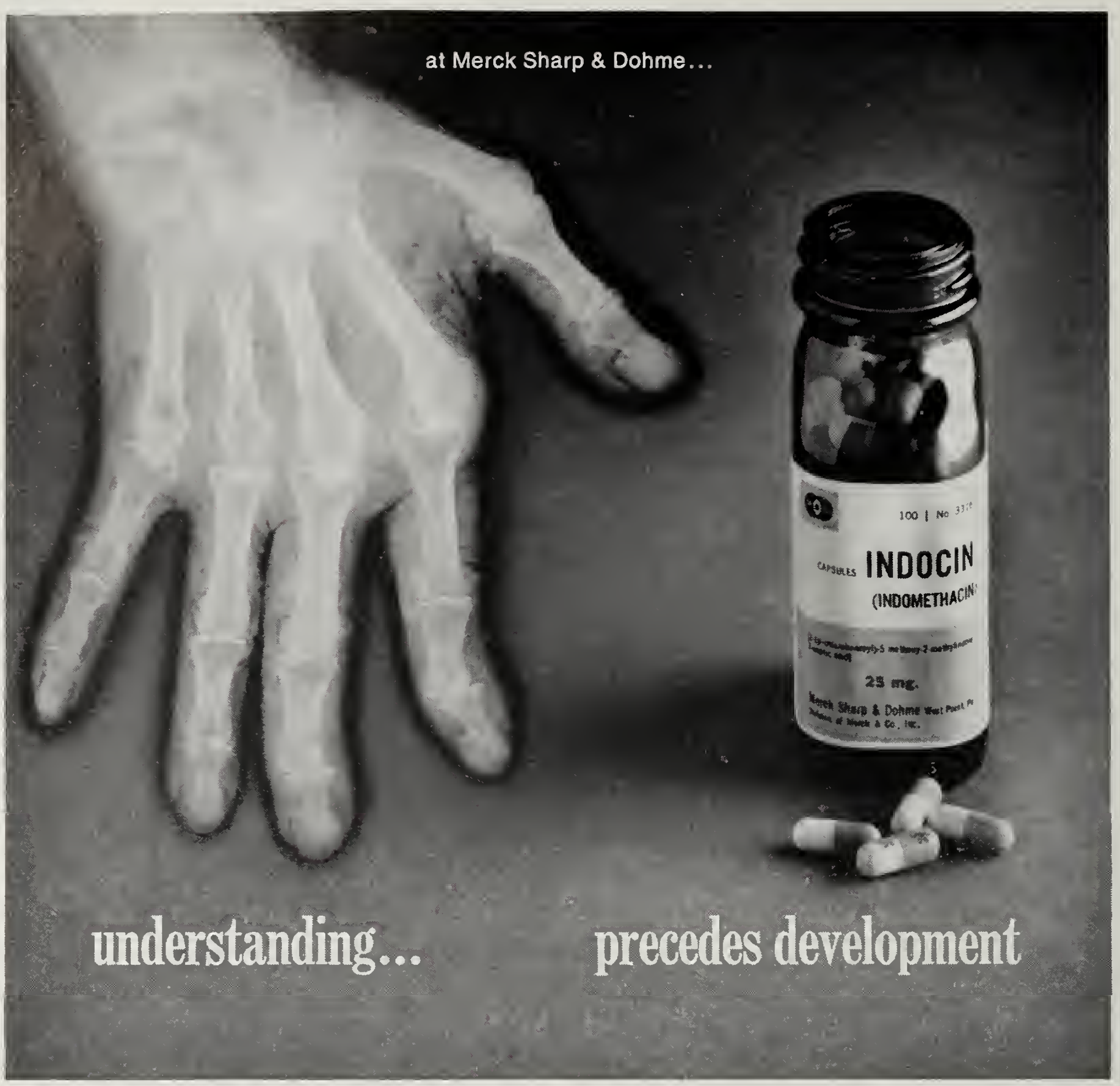
* Resignations are accepted without prejudice only upon payment of dues for the year in which resignation is requested.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Warning: Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles, machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism.
Precautions and Adverse Reactions: Most commonly, headache, dizziness, lightheadedness, G.I. disturbances. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Rare reports of effects not definitely known to be attributable to INDOCIN include bleeding from the sigmoid colon (either from a diverticulum or without a known previous pathologic condition), perforation of preexisting sigmoid lesions (diverticulum, carcinoma), and hematuria. In other rare cases, a diagnosis of gastritis has been made while the drug was being given. One patient developed ulcerative colitis, and another, regional ileitis, while receiving INDOCIN; when the drug was given to patients with preexisting ulcerative colitis, there was an increase in abdominal pain. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, edema, and hypersensitivity reactions. Slight BUN elevation, usually transient, has been seen in some patients, although the preponderance of evidence indicates that INDOCIN does not adversely affect renal function, even in patients with preexisting renal disease. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Leukopenia has been seen in a few patients. Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values; the relationship of these changes to the drug, if any, has not been established. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity. Before prescribing or administering, read product circular with package or available on request.

Dr. David M. French was reinstated to Active membership upon payment of 1965 dues. Drs. Erwin G. Pese and Charles R. Webb were reinstated to Associate membership.

Committee on Occupational Health: Dr. Young, Chairman of this Committee, was present to present the Committee's recommendation to the Executive Board that the Workmen's Compensation Fee Schedule be increased. He also stated that the insurance companies writing compensation coverage had decided, because of fear of antitrust suit, to no longer coöperate in the preparation of a fee schedule. In the past this schedule has been a joint venture, the insurance companies being represented by the Washington Claims Managers' Council. The consensus was that from now on in all fee negotiations the new Relative Value Scale be used as a base and that Dr. Young select members of the Committee on Occupational Health to meet with Dr. Frank S. Bacon and representatives of the Relative Value Study Committee to prepare a revision of the Workmen's Compensation Fee Schedule so that such revision will be in accord with the new Relative Value Scale.

Committee on Environmental Health: A statement on the subject of air pollution (see page 559), prepared by this Committee with the assistance of Dr. Eloise W. Kailin, was approved as presented, and for such release as may be useful, with commendation to the Committee for its efforts to stimulate interest in the problems of air pollution and activities which may reduce air pollution in D. C.

Cancer Study Committee: The request from the Committee presently conducting the Study on Sigmoid Colon and Rectal Cancer that "complete academic freedom be afforded the Committee in the publication of its report based on complete findings of the study" was approved.

Committee on Smoking and Health: The following amended policy statement regarding the sale of cigarettes and smoking in hospitals was approved: "That the Executive Board communicate with all local hospitals suggesting that hospitals not permit the sale of cigarettes and that physicians and employees in hospitals not smoke in public areas of a hospital. Further, it is the desire of the Medical Society to seek to discourage patients from smoking while in a hospital."

GHI and the Hospital Council: Drs. Ecker and Coffey reported on the status of the negotiations between Group Hospitalization, Inc. and the Hospital Council. At a meeting attended

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by them recently, it seemed that a compromise had been reached agreeable to both groups. Shortly thereafter, however, a news release indicated that no compromise had been reached. In view of the fact that the Executive Board at its last meeting had voted to send a letter to GHI and the presidents of the boards of the local coöperating hospitals indicating its concern over the situation, it was agreed that the Executive Board should continue to evidence an interest in and a desire to settle this entire matter so that this lack of understanding between the 2 groups might be resolved for the best interests of all concerned, particularly, the public.

Medical Records in Hospitals: A letter received concerning the reduction of complexity of medical records in hospitals was reviewed and it was voted to refer this matter to the Committee on Liaison with Hospitals and Medical Schools, with a request that the Committee review the situation in the light of the requirements of the Commission on Accreditation of Hospitals and report back to the Executive Board.

New Consulting Editor: At the request of Dr. Wallace M. Yater, Editor of the MEDICAL ANNALS, the Executive Board confirmed the appointment of Dr. Leon Laster, Chief of the Section on Gastroenterology, National Institute of Arthritis and Metabolic Diseases, as Consulting Editor to replace Dr. Vernon Knight.

Miscellaneous Business

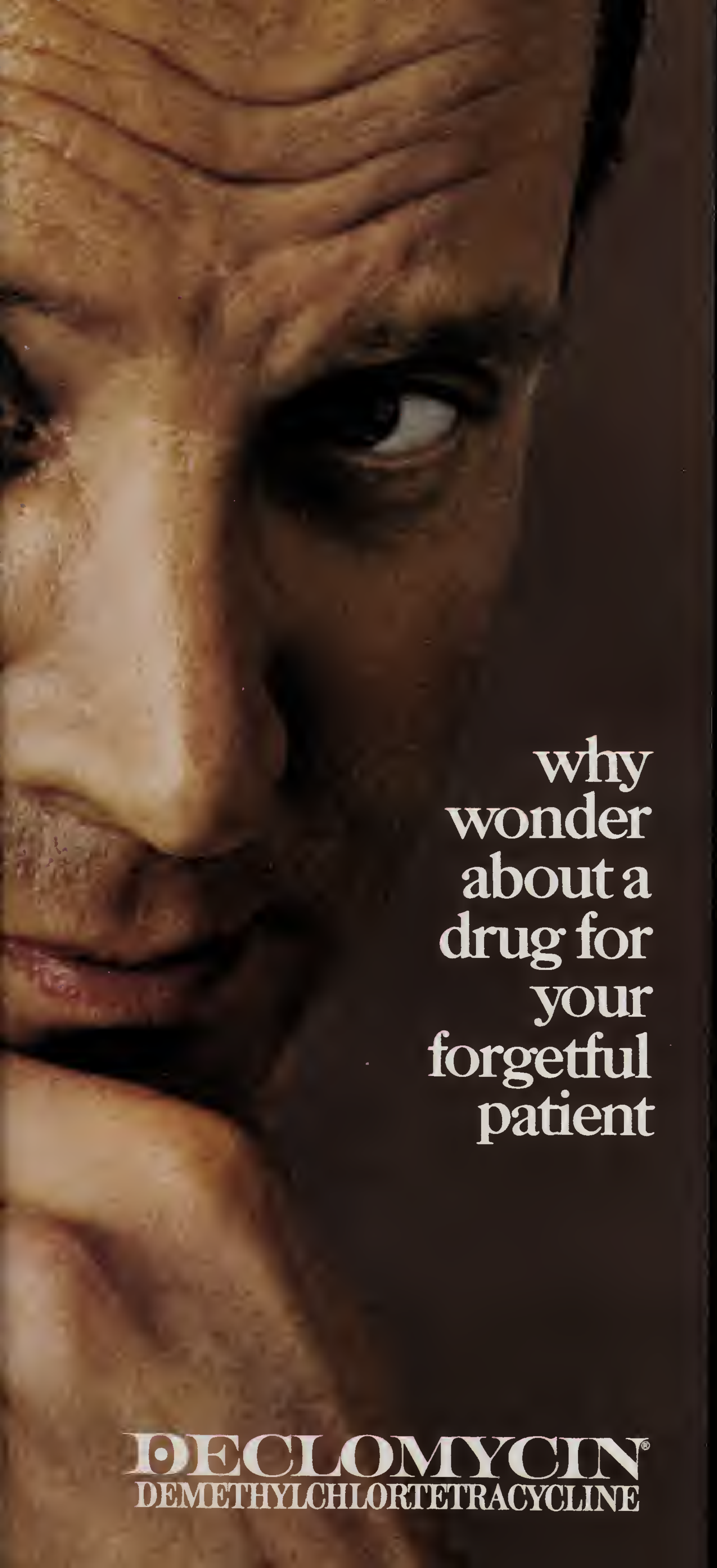
Dr. Holden reviewed the actions taken at the AMA meeting, held in June in Chicago, and agreed to provide a copy for publication in the MEDICAL ANNALS (see September issue, pages 495–500).

The following recommendations of the Committee on Child Welfare were approved:

1. That, for the record, in the Committee's opinion the administrative authority for the school health service should remain with the D. C. Department of Public Health until such time as the facts show a need for change.

2. That the Medical Society request funding from the Department of Health, Education, and Welfare to obtain an outside consultant to make a comprehensive analysis and submit to the Society recommendations for improvement of the school health program.

The Secretary reported that some 1,300 members had had their pictures taken in anticipation of a new composite. This is twice the number contained in the last composite and would require



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Precautions and Side Effects—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. Use of demethylchlortetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long-term use but has also been observed in short treatment courses. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment. Side reactions include glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and dermatitis. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Anaphylactoid reactions have been reported.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products.

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3 or 4 large frames for which there is little or no wall space available. As an alternative, he suggested a directory of the membership to contain these pictures together with the physician's name, medical school, specialty, Board certification, office address, and telephone number. He requested authority to proceed and to determine the possibility of financing much of the cost through advertising. The Secretary was empowered to proceed with the development of the directory and to seek acceptable advertising to support the costs.

There being no further business, the meeting was adjourned.

Meetings

The American College of Physicians will hold its **18th Annual Regional Meeting** for specialists in internal medicine in Maryland and the District of Columbia on Saturday, October 15, in the Exhibit Hall of the D. C. Medical Society Headquarters Building.

The first part of the morning session, 9:00 to 11:00 a.m., will be provided by the George Washington University School of Medicine. The remainder of the morning and the entire afternoon program will be devoted to papers of current interest by members and guests of the College from the Washington area.

Dr. R. H. Kampmeier, of Nashville, Tenn., President-elect of the College and Professor of Medicine Emeritus at Vanderbilt Univeristy School of Medicine, will be the guest speaker at the luncheon in the State Room of the Mayflower Hotel.

The meeting is under the joint direction of Dr. Thomas W. Mattingly, Governor of the College for the District of Columbia, and Dr. Martin L. Singewald, ACP Governor for Maryland. A cordial invitation to attend is extended to all Fellows and Associates of the College and to all physicians, residents, and interns in Washington and vicinity.

The Nation's women physicians will convene in Washington, November 2–5, for the **1966 Annual Meeting of the American Medical Women's Association.** The International Inn is the headquarters hotel for the business and scientific meetings.

"Sexual Problems in Clinical Practice" will be the subject of the Scientific Symposium for Saturday morning, November 5, beginning at 10 a.m. Speakers will include David Reed, Ph.D., of Tulane University; Richard H. Klemer, Ph.D., University of Washington; Edward J. Hornick, M.D., Albert Einstein College of Medicine; Edward M. Litin, of the Mayo Clinic; Martin Goldberg, M.D., University of Pennsylvania; and Clark E. Vincent, Ph.D., Bowman-Gray School of Medicine. The speaker at the luncheon following this session will be David R. Mace, Ph.D., Executive Director of the American Association of Marriage Counselors; the subject of his address, "Men, Women and Marriage."

Dr. Elizabeth A. McGrew, of Chicago, will be inaugurated as President, succeeding Dr. Margaret J. Schneider, of Cincinnati, at the reception and banquet, November 4. Dr. Alice Drew Chenoweth, of Arlington, Va., is serving this year as First Vice President of AMWA. She is an Active member of the D. C. Medical Society.

Because the **60th Annual Meeting of the Southern Medical Association** will convene in Washington, November 14–17, 1966, the Medical Society of the District of Columbia is foregoing its usual Annual Scientific Assembly in order to participate in the SMA meeting. The meeting place will be the Washington Hilton Hotel.

Twenty-two Scientific Sections of SMA will each present its own program. There will be special symposia, scientific and technical exhibits, the President's Luncheon, the President's Night-dinner-dance, alumni reunions, conjoint society meetings, a golf tournament, scientific color TV, and entertainment for the women.

Dr. J. Garber Galbraith, of Birmingham, Alabama, is President of the SMA. The President-elect, Dr. Guy T. Vise, Meridian, Miss., will take office at this meeting. Dr. Oscar B. Hunter, Jr., First Vice President of the Association, and Dr. George P. Blundell, a member of the Council and Chairman of the Section on Pathology, are in charge of local arrangements.

Other members of the Medical Society who will participate actively in the meeting are the following Section officers: Dr. Irving B. Brick, Vice Chairman, Section on Gastroenterology; Dr. James J. Feffer, Vice Chairman, Section on Medicine; Dr. James G. Sites, Chairman, Section on Obstetrics; Dr. William J. G. Davis, Vice Chairman, Section on Ophthalmology; Dr. William J. Tobin, Vice Chairman, Section on Orthopedic and Traumatic Surgery; Dr. William M. Trible, Vice Chairman, Section on Otolaryngology; and Dr. A. F. Castro, Vice Chairman, Section on Proctology.

The 20th Clinical Convention of the American Medical Association will convene in Las Vegas, November 27–30. The 4-day meeting will include scientific sessions on 18 major topics, 3 postgraduate courses, breakfast roundtable conferences, closed-circuit TV, medical motion picture programs, and scientific and industrial exhibits.

Postgraduate courses have been expanded to 3 topics: Obstetrics and Gynecology, Fluid and Electrolyte Balance, and Cardiovascular Disease. Each course will consistof 3 half-day sessions and there will be a $10 registration fee for each course.

The AMA House of Delegates will meet in the Dunes Hotel and Caesar's Palace.

Advance registration for the Convention can be made with the Circulation and Records Department of the AMA, 535 North Dearborn Street, Chicago, Ill. 60610. Hotel reservations should be made with the AMA Housing Bureau, Las Vegas Convention Bureau, Convention Center, Paradise Road, Las Vegas, Nev.

The Eighth National Conference on the Medical Aspects of Sports will be held in conjunction with the Clinical Convention. The meeting will be held on Sunday, November 27, at Caesar's Palace and will be devoted to a discussion of problems faced by team physicians at all levels of athletic competition.

General News

The Washington Society for the History of Medicine, formed in 1961, holds bi-monthly meetings except during the summer months. The Society, which is an affiliate of the American Association for the History of Medicine, invites membership of physicians in the Washington area who are interested in the history of medicine. The officers for 1966–67 are:

Dr. Mark N. Ozer, *President*; Dr. Zigmond M. Lebensohn, *Vice President*; Dr. William C. Roberts, *Secretary*; and Mr. Louis P. Hellman, *Treasurer*.

Those interested in becoming members and receiving notices of meetings should write to Dr. Roberts, Building 10, Room 6N252, Clinic of Surgery, National Heart Institute, Bethesda, Md. 20014, or telephone 496-4711.

SYMPOSIUM ON ADOLESCENCE

NEW ORLEANS, LOUISIANA DECEMBER 1–3, 1966

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GUEST LECTURERS INCLUDE:

Dana Farnsworth, M.D., Director of Student Health Services at Harvard University, Cambridge, Mass.

Irvin Kraft, M.D., Professor of Child Psychiatry at Baylor Medical School, Houston, Tex.

John Schimel, M.D., Associate Director of William Alanson White Institute of Psychiatry, Psychoanalysis and Psychology, New York, N. Y.

George Tarjan, M.D., Professor of Psychiatry and Program Director of Mental Retardation Project at University of California in Los Angeles, Calif.

Carroll Witten, M.D., President-elect of American Academy of General Practice, Louisville, Ky.

AMONG TOPICS TO BE DISCUSSED:

"The Physician's Role in Mental Retardation"
"Parents of Problem Children"
"Handling of Adolescents by General Practitioners"
"Sexual Morality—A College Dilemma"
"Drugs in the Treatment of Children and Adolescents"
"Learning Problems of the Adolescent"
"Adolescence and Social Mores"
"Talking About Sex with Adolescents"
"Religious-Psychological Conflicts"

Symposium will be held at the Fontainebleau Motor Hotel, 4040 Tulane Ave., New Orleans. Early hotel reservations are recommended.

Gene L. Usdin, M.D., *Director of Psychiatric Services*
Touro Infirmary, 1400 Foucher Street, New Orleans, Louisiana 70115

Enclosed is my registration fee of $20 for the SYMPOSIUM ON ADOLESCENCE to be given December 1–3, 1966 at the Fontainebleau Motor Hotel. (Checks should be made payable to Touro Infirmary.)

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The Division of Urology of Georgetown University School of Medicine has been awarded a $203,000 research grant for the study of methods to prevent kidney disease leading to death in pediatric and adult patients with various forms of neurologic diseases. The grant, which covers a 3-year period, was awarded by the Kidney Disease Branch of the Public Health Service, NIH, Department of Health, Education, and Welfare. The study will be carried on under the direction of Dr. Roger Baker, Professor and Director of the Division of Urology.

George Washington University School of Medicine has received a grant of $59,128 from the John A. Hartford Foundation, Inc. of New York, to continue a study of the body's natural defense mechanisms to certain chronic diseases. The 2-year study will be directed by Dr. Robert C. Parlett, Professor and Chairman of the Department of Microbiology.

Doctors Hospital announces that the services of this hospital are available and are being rendered to white and Negro patients as well as to patients of other origins. In other words, patient admission, placement in the hospital, and treatment are conducted without regard to race, creed, color, or national origin. The policy of civil rights conformity is being actively supported by the members of the medical staff as well as by the admitting office and other administrative units.

Colonel Charles H. Moseley, MC, USA, has been appointed Director of the American Medical Association's Department of Government Medical Services. He took office in August, after retiring from active duty on the staff of the U. S. Army Surgeon General. Among his responsibilities at the AMA will be the administration of the Volunteer Physicians for Vietnam program. His department will also furnish additional liaison for the AMA with the various Federal agencies responsible for the administration of Public Law 89-97.

Personals

Dr. Roland B. Scott, Chief Pediatrician at Freedmen's Hosptial, was presented the Distinguished Service Award for 1966 at the Pick-Congress Hotel in Chicago during the 71st Annual Meeting of the National Medical Association, August 7–11. He was cited for research activities in the fields of sickle-cell anemia, pediatric allergy, and growth studies involving infants and children. These and other studies have been recorded in over 130 publications in the medical literature. The citation included other accomplishments, such as his 25 years' service on the faculty of Howard University College of Medicine.

DR. ROLAND B. SCOTT is wearing the Distinguished Service Medal which he has just received from Dr. Marshall F. Nichols, of Cincinnati, Ohio, Chairman of the Award Council of the National Medical Association.

Dr. Scott was credited with leadership in the integration of the Negro physician, particularly in the field of pediatrics. The Department of Pediatrics at Howard University, which he heads, was the first to participate at Gallinger Municipal (now D. C. General) Hospital in the medical student program. He was the first Negro pediatrician to be named to the staff of the Children's Hospital of D. C., the first Negro physician in the United States to be certified by the American Board of Pediatrics, and the first Negro pediatrician to be admitted to membership in the American Pediatric Society and the Society for Pediatric Research. He is currently serving as Vice President of the American Academy of Allergy and Secretary to the Section on Allergy of the American Academy of Pediatrics. He is an alumnus of Howard University.

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THE BOAR'S HEAD INN
Charlottesville, Virginia

Colonel John Boyd Coates, Jr., assumed command of Valley Forge General Hospital at Phoenixville, Pa. on September 1. He was assigned to Valley Forge after a 2-year tour of duty as Deputy Surgeon of the U. S. Army in Europe. As Director of the Army Medical Service's Historical Unit, 1954–1964, he was also editor-in-chief of the Official History of the Army Medical Department in World War II and Korea. Colonel Coates is an Associate member of the D. C. Medical Society.

Dr. Frank N. Miller, Jr., has been named Associate Dean for Student and Curricular Affairs **and Dr. Alvin E. Parrish** was named Director of Clinical Research at George Washington University School of Medicine, effective September 1.

Dr. Miller, Professor of Pathology, will be responsible for the medical admissions office and for management of student financial aid. He will continue to teach in the Department of Pathology.

Dr. Parrish will devote full time to teaching and research. As Director of Clinical Research he will coördinate these activites in the University Hospital and Clinics. He will be responsible for the new research floor of the Meyer Pavilion and its Carr Memorial Research Laboratories and will assist in training ancillary personnel in investigative techniques.

Both physicians are George Washington alumni.

Dr. Murray M. Copeland has been appointed to the National Advisory Cancer Council by the Surgeon General of the Public Health Service, William H. Stewart, for a 3-year period. Dr. Copeland is Associate Director for Education, Professor of Surgery (Oncology), and General Surgeon at the University of Texas M. D. Anderson Hospital and Tumor Institute in Houston. Before joining the Anderson Hospital and Tumor Institute in 1960, he was Professor and Chairman of the Department of Oncology at Georgetown University School of Medicine. This appointment marks the second time Dr. Copeland had served on the Council, having been a member from 1950 to 1961. He has retained his Associate membership in the D. C. Medical Society.

Dr. Andrew A. Marchetti took office as President of the American Gynecological Society at its meeting in Hot Springs, Va., June 2–4.

Dr. Arthur Dick took office, July 1, in Chicago, as President of the American Society of Maxillofacial Surgery.

Dr. Robert H. Barter was reëlected Secretary of the Section on Obstetrics and Gynecology of the American Medical Association at its recent business meeting in Chicago, June 29.

Physicians who wish to appear on the scientific program of the Section on Obstetrics and Gynecology at the 1967 Annual Convention of the AMA should correspond with Dr. Barter. His address is 901 23rd Street, N.W., Washington, D. C. 20007.

Dr. Lester S. Blumenthal was elected Vice President of the American Association for the Study of Headache at its annual meeting in Chicago, June 25.

Dr. J. Earl Kadan was elected Chairman **and Dr. James C. Walsh,** Vice Chairman, for the District of Columbia of District IV, the American College of Obstetricians and Gynecologists. The election took place at the Palmer House in Chicago, April 29. The officers will serve until the fall of 1969.

During the month of July, **Dr. Ernest Gould** represented Medico in Honduras, where he lectured and performed surgery.

Dr. Lillian G. Wheeler has been elected to fellowship in the American College of Obstetricians and Gynecologists.

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1. Riese, J.A.: Amer. J. Gastroent. 28:541 (Nov.) 1957

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An ad hoc committee of the Woman's Auxiliary to the Medical Society of the District of Columbia met at the home of Mrs. Wallace M. Yater on July 5 to explore what can be done to reactivate the program for foreign interns and residents in the hospitals of the District of Columbia. There is great interest on the part of the leaders of the Auxiliary to coöperate with the International Visitors Service Council (IVIS) on this project, which includes English lessons, information, home hospitality, and other services as requested.

Mrs. Jed W. Pearson, Chairman of the Auxiliary's International Committee, will head the project. She will work with Mrs. Thomas N. Carter, President of the Auxiliary, Mrs. Dean E. Brown, Mrs. John C. McClintock, Mrs. William Shuler, and other interested persons and committee appointees. Mrs. Pearson will endeavor to secure a representative from the Women's Board of each hospital. The Wives of Student American Medical Association (WSAMA) will be contacted and their assistance solicited.

The Executive Office of the D. C. Medical Society is coöperating by securing lists of the foreign interns and residents on the hospital staffs as of July 1, 1966. IVIS has information kits, already assembled, ready for distribution.

The committee hopes to have plans well under way by early fall.

Obituaries

Fred August Moss, A.B., M.A., Ph.D., M.D.

(1893-1966)

A TRIBUTE

With the passing of Dr. Fred A. Moss something irreplaceable has gone from the lives of so many who came in contact with him.

He came to Washington in 1921 to teach psychology at the George Washington University. In his classes were premedical students, many of whom are now practicing in the District of Columbia. Some readily attribute to him their inspiration to pursue the study of medical science or their determination to train themselves for professional achievement in medicine.

In his research Dr. Moss was a true scientist. What apparatus he needed he and his students built. Most of his research was done in the pre-research grants era, nor did his research have the advantage of complicated computer methods customary for so much research today. Yet a number of his studies were real "firsts." One was his development of a scientific method of measuring motivation in animal experimentation, still in wide use in psychological and physiological laboratories today. His development of a scholastic aptitude test began at George Washington University Medical School, with the Class of 1932, and led to the foundation of an Aptitude Test Committee in the Association of American Medical Colleges. This work was the forerunner of the entrance testing program ultimately established for all medical schools.

FRED A. MOSS, M.D.

In 1936 Dr. Moss left the University to pursue his interests in other settings. During a number of years he devoted his energies primarily to the study of mental illness. Although his views of mental illness were biological, his treatment of his patients had a strong psychological touch, which kept many a long-ago "cured" patient looking back to him for guidance, or occasionally coming to him for inspiration, encouragement, or just discussion of the events of life.

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Past the age at which the average person has reached his peak of accomplishment, Dr. Moss pursued yet another field of endeavor—that of finance and financial management. He often said that his first love was psychology and he took this with his understanding of human nature to the study of the stock market, and the organization and management of companies in which he invested.

Mindful of his medical colleagues who often asked his advice on financial matters, a few years before his death he wrote a brochure which was widely distributed by the investment firm of Merrill Lynch, Pierce, Fenner and Smith, entitled "Two Dozen Clues for the Doctor's Successful Investments."

Despite his extremely full and busy professional life, from his boundless energy and enthusiasm Dr. Moss had some time left over to devote to hobbies. He loved roses, and the extensive rose garden which he developed and tended gave evidence of the enjoyment, peace and tranquillity which such beauty of nature was able to give him. He was also a Shakespeare enthusiast. He liked poetry and often wrote, in Omar Khayyam style, verses to express his own feelings and philosophy of life. In the spirit of Omar, on life's fast-fading dreams, he wrote:

"Though Spring too quickly goes and takes the Rose,
And Love's brief day, also, too soon doth close;
Yet if we had no Spring, no Rose, nor Love,
Our life would be a book of dullest prose."

Thelma Hunt, Ph.D., M.D.

Dr. Fred A. Moss, educator, psychologist, physician, and researcher, died, July 27, 1966, at his home, 700 St. Stephens Road, Alexandria, Va.

Dr. Moss was born in Hayesville, N.C., August 31, 1893 to James M. and Ora Russell Moss. He graduated from Mercer University in 1913, received his Master's degree from Columbia in 1920, a doctorate in psychology from George Washington University in 1923, and his medical degree, also from George Washington, in 1927.

The first part of his career was in teaching and educational work. From 1913 to 1917 he was Superintendent of Schools in Alma, Ga. He served on the faculty of George Washington University as Professor of Psychology from 1921 to 1936. From 1936 to 1942 he owned and operated the Moss Sanitarium for Mental and Nervous Diseases in Alexandria.

Dr. Moss was one of the first men in this country to devise a standardized test for automobile drivers. In 1926 he served as Secretary of the Hoover Commission on the Causes of Automobile Accidents. He was Assistant Alienist for the District of Columbia from 1929 to 1935, Director of Physiological Studies for the Society of Automotive Engineers from 1929 to 1935, and Director of Medical Aptitude Tests for the Association of American Medical Colleges from 1929 to 1947.

He was a member of the American Medical Association, the American Association for the Advancement of Science, the American Psychological Association, and the American Medical Editors' and Authors' Association. Elected to Active membership in the Medical Society of the District of Columbia in 1928, he became a Life member in 1965. He was a member of the National Society for the Promotion of Biological and Physiological Psychiatry and the Southern Association of Philosophy and Psychology.

He published many articles and books and served as editor of the Prentice-Hall books in psychology. His writings included the "Applications of Psychology" (1929), "A Psychology for Nurses" (1934), "Foundations of Abnormal Psychology" (1932), and "Comparative Psychology" (1934). Recently he published "The Pursuit of Happiness," a book of poems which reflected his own philosophy of life.

His wife, Mrs. Catharine Summers Moss, survives him, together with a daughter, Miss Fredericka C. Moss, of the home. He also leaves a daughter, Dr. Claudine Moss Gay, and a son, Dr. James M. Moss, both members of the Medical Society of the District of Columbia.

Floyd Sterling Rogers, Jr., M.D.

(1906-1966)

Dr. Floyd S. Rogers, specialist in obstetrics and gynecology in Washington for many years, died, May 7, 1966 in Columbia, S. C.

Dr. Rogers was born in Coleman, Ga., September 12, 1906. He graduated in medicine from Tulane University in 1932. After interning for a year at Grady Hospital, Atlanta, Ga., he went to New York City to serve a 3-year residency in obstetrics and gynecology at New York Hospital of Cornell Medical College. The following year, 1937-38, he continued his training at the Free Hospital for Women at Harvard Medical School, Boston.

Dr. Rogers began his practice in the District of Columbia in 1938. For many years his offices were located at 1150 Connecticut Avenue, N.W.

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In 1964 Dr. Rogers discontinued his private practice to become a full-time physician with the Veterans Administration Central Office in Washington, D. C. A year ago he moved to Columbia, S. C. to accept a position on the staff of the Palmetto State Hospital.

Dr. Rogers was a diplomate of the American Board of Obstetrics and Gynecology. He was a Fellow of the American College of Surgeons, a Fellow of the International College of Surgeons, and a member of the American Medical Association, the Washington Gynecological Society, the Osler Society, and the Pan American Medical Society. He had been an Active member of the D. C. Medical Society since 1938.

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Desquamative Interstitial Pneumonia—Young, Johnson and Bell

(*Continued from page 540*)

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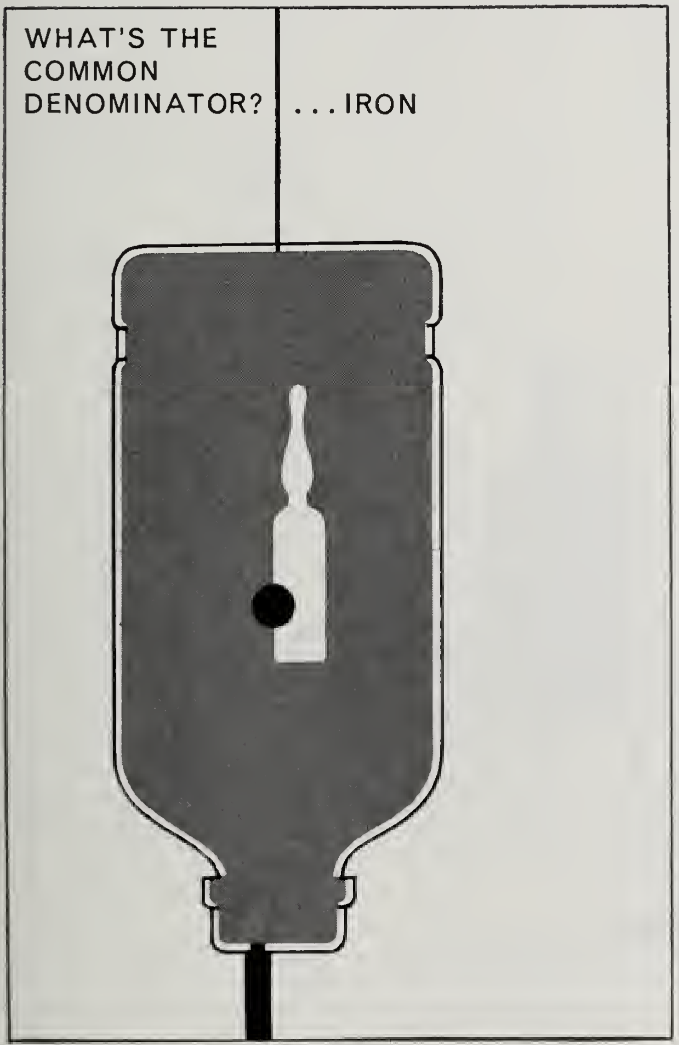

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SIDE EFFECTS: Local and systemic side effects are few. Staining of the skin may occur. Excessive dosage, beyond the calculated need, may cause hemosiderosis. Although allergic or anaphylatoid reactions are not common, occasional severe reactions have been observed, including three fatal reactions which may have been due to Imferon (iron dextran injection). Urticaria, arthralgia, lymphadenopathy, nausea, headache and fever have occasionally been reported.

PRECAUTIONS: If sensitivity to test doses is manifested, the drug should not be given. Imferon (iron dextran injection) must be administered by deep intramuscular injection only. Inject only in the upper outer quadrant of the buttock, not in the arm or other exposed area.

CONTRAINDICATIONS: Imferon (iron dextran injection) is contraindicated in patients sensitive to iron dextran complex. Since its use is intended for the treatment of iron deficiency anemia only it is contraindicated in other anemias.

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BOOK REVIEWS

Current Therapy 1966. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D., with 12 consulting editors. Price, $13.00. Pp. 857. Philadelphia: Saunders, 1966.

The 1966 volume comprises methods of treatment by 317 authorities from all over the world. The type and layout are comfortable to the eyes, and the index is more accurate than in previous editions.

For the specialist in internal medicine the sections on the chronic diseases are not as valuable as the sections on the more acute situations.

Treatment programs are up to date. Indeed, on page 331 allopurinol was described as "the drug of choice" for its uricosuric effect in gout. At the time of this review the drug is not on the market. Before such a sweeping statement is made, a drug should be in broad use for many months. However, this reflects the enthusiasm of only one author, as most sections advise caution with new products.

Quick references to normal laboratory values are available on the inside of both covers.

Two months ago I gave a copy to the emergency room of a very busy downtown general hospital. The interns and residents have dog-eared this copy, which is referred to 24 hours a day. It is in this type situation that "Current Therapy" is most valuable. Every emergency room and every physician in any remote area would be benefited by this ready reference book.

Charles Waters Thompson, M.D.

The Addict and the Law. Alfred R. Lindesmith, M. A., Ph.D. Price, $7.50. Pp. 337. Bloomington, Ind.: Indiana University Press, 1965.

The author has been a long-time observer of the narcotics problem. He has studied the situation here and abroad as well as conducted research in the law and behavioral science programs at the University of Chicago. Now, after 30 years of studying the problem he recommends that drug addiction be treated as a disease. He believes the present U. S. policy of prohibition actually contributes to the spread of the habit by creating a lucrative black market in illicit drugs. His reason is based on analysis of the results of prohibitory policies in this country and in areas of the Far East, where narcotic addiction is handled as a crime and is widespread, as contrasted with those in England and in Western Europe, where legal access to narcotic drugs is permitted, under medical supervision. There, he finds, addiction is not a major social problem.

The author points out that our present program of handling the drug problem was established by the U. S. Treasury Department officials, and the basic anti-narcotics statute in the United States, the Harrison Act of 1914, was passed primarily as a revenue measure. He concludes that our present system of control is unjust to addicts and actually intensifies the social evils that it is intended to mitigate. As an alternative the writer proposes a program of gradual reform leading to a genuinely medical approach to addiction. He exercises the hope that because of the increasing public and professional interest in the problem the attitude of law enforcement officers will change so that drug addiction may be treated as a disease.

There are 10 chapters dealing with such subjects as Narcotic Clinics, Control, Strategy of Enforcement of the Narcotic Act, Obstacles and Patterns of Reform, etc. Space for notes provided with each chapter and the index make this book valuable as a reference.

John R. Pate, M.D.

Drug Abuse. A Manual for Law Enforcement Officers. Prepared under the direction of James B. Landis, M.D., and Donald K. Fletcher. Pp. 55, illustrated. Philadelphia: Smith, Kline & French, 1965.

This is a short manual which is very helpful in the understanding of drugs subject to abuse. There is an explanation of terminology of the drug user and a glossary of terms in the appendices. Security measures, investigative techniques, and the illegal traffic in dangerous drugs are discussed in the text.

The writers with the aid of a distinguished advisory panel have prepared a most informative manual which should prove of value for the medical profession as well as for law enforcement officers. It supplements the book, "The Addict and The Law."

John R. Pate, M.D.

Pathology, 5th ed., in 2 volumes. Edited by W. A. D. Anderson, M.A., M.D., F.A.C.P., F.C.A.P. Price per set, $21.00. Pp. 1439, with 1260 illustrations and 7 color plates. St. Louis: Mosby, 1966.

This is the fifth edition of a well-established text of pathologic anatomy. This year the book appears in 2 volumes, which makes it more convenient to use. Also the subject matter is listed on the front cover of each volume, which saves time when looking for a particular subject. The approach to the study of disease is a classical one, as recorded in textbooks of pathology, with the advantage of having the various chapters

(*Continued on page 42*)

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Book Reviews

(*Continued from page 40*)

written by experts in their particular field. Without exception each chapter is well written and illustrated. It is highly recommended as a reference in pathology for medical students, pathologists, and clinicians.

VERNON E. MARTENS, M.D.

Ciba Foundation Study Group No. 22: Gonadotropins: Physicochemical and Immunological Properties. Edited by G. E. WOLSTENHOLME, O.B.E., F.R.C.P., F.I. Biol., AND JULIE KNIGHT, B.A. Price, $3.50. Pp. 125, with 28 illustrations. Boston: Little, 1966.

The Ciba Foundation is an international institution which, amongst its activities, organizes small conferences on scientific subjects and records the informal presentations and discussion of participating scientists in volumes such as this.

In February 1965 over 20 research workers of prominence, comprising the Study Group on Gonadotropins, met and discussed the advances and problems relative to biochemical and immunological study of the gonadotropins, resulting in this small but excellent volume. The appeal of this book will, of course, be limited to those interested in research endocrinology and familiar enough with laboratory techniques to appreciate the delicate and subtle means by which these hormones are being separated, purified, characterized, and measured. Minimal mention is made of the clinical aspects of the subject.

The period of important biological research into the gonadotropins began about 40 years ago, but great new impetus was injected with the commencement of the "Immunological Era" in 1960. In this conference heavy emphasis is placed on the immunological approaches, particularly in the area of hormone assay. Free-wheeling discussion throughout the volume permits a consensus of approach to many of the knotty problems common to the researchers.

This book is highly recommended to those interested in and familiar with gonadotropin research.

GILBERT E. HURWITZ, M.D.

CIBA Foundation Symposium: Preimplantation Stages of Pregnancy. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., F.R.C.P., F.I.BIOL., AND B. A. O'CONNOR. Price, $13.50. Pp. 430, with 153 illustrations. Boston: Little, 1965.

This is another volume in a distinguished series reporting conferences of investigators in special subjects. This particular conference concerns the biology of the mammalian egg during the week or more elapsing between release from the ovary and attachment in the uterus. During this time there occurs meiotic reduction to haploid of the chromosomes supplied by the mother, restoration of the diploid complement following fertilization, release of the zygote from the eggshell-like zona pellucida, and multiple cell divisions leading to differentiation of trophoblast and to development of the embryo to the stage of blastocyst.

This book reports experimental manipulation of mouse and rabbit eggs, principally by tissue culture and transplantation technics, and makes virtually no mention of the human egg. The book will therefore appeal to 2 types of readers, the one-in-a-thousand experimental biologist and the medical or paramedical specialist interested in future breakthroughs in basic research bearing on the control of human reproduction.

Phenomena investigated include the following: "capacitation" of sperm by an unidentified factor in the maternal genital tract, rupture of the zona, transfer of maternal antigens to the zygote during passage of the latter through the salpinx, and acceleration or slowing of the transport of zygotes along the tube. Control of any of these events might revolutionize either "planned parenthood" or medical treatment of sterility.

The reviewer of this book happens to be more interested in the clear implications of some of the reported experiments that some double ovum twins may be monochorionic (and vice versa) and that some mammalian mosaics may have a relatively thorough mixture of cell strains within their organs, rather than the segmental distribution observed in insects.

A book for the armchair philosopher, if not for the clinician.

HENRY W. EDMONDS, M.D.

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October 21–25: American Heart Association. Americana Hotel, New York. Address: Mr. Rome A. Betts, *Executive Director*, 44 East 23rd Street, New York, N. Y. 10010.

October 22–27: 35th Annual Meeting of the American Academy of Pediatrics. Palmer House, Chicago. Address: Dr. E. H. Christopherson, *Executive Director*, 1801 Hinman Avenue, Evanston, Ill. 60204.

October 23–26: American College of Gastroenterology. October 27–29: Annual Postgraduate Course. Bellevue-Stratford Hotel, Philadelphia. Address: Mr. Daniel Weiss, *Executive Director*, 33 West 60th Street, New York, N. Y. 10023.

November 2–5: American Medical Women's Association. International Inn, Washington. Address: Mrs. Gertrude F. Conroy, Executive Director, 1790 Broadway, New York, N. Y. 10019.

November 6–9: Medical Society of Virginia. Williamsburg Lodge, Williamsburg, Va. Address: Mr. Robert I. Howard, *Executive Secretary*, 4205 Dover Road, Richmond, Va. 23221.

November 7–9: Association of Military Surgeons of the United States. Washington Hilton Hotel, Washington. Address: Brig. Gen. Frank E. Wilson, USAR (Ret.), Executive Director, 1500 Massachusetts Avenue, N.W., Washington, D. C. 20005.

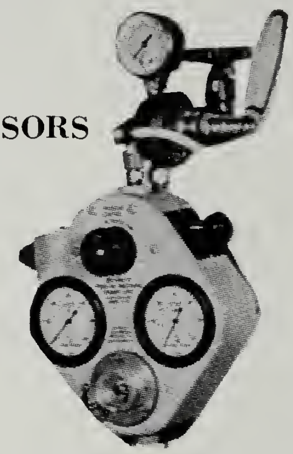
November 7–11: PAHO/WHO International Conference on Vaccines Against Viral and Rickettsial Diseases of Man. Pan American Health Organization Building, Washington. Address: Dr. M. Martins da Silva, Office of Research Coördination, Pan American Health Organization, 525 23rd Street, N.W., Washington, D. C. 20037.

November 11–12: Association of Clinical Scientists. International Inn and the Washington Hospital Center, Washington. Address: Dr. Robert P. MacFate, Secretary-Treasurer, 300 North State Street, Chicago, Ill. 60610.

November 14–17: Southern Medical Association. Washington Hilton Hotel, Washington. Address: Mr. Robert F. Butts, Executive Director, 2601 Highland Avenue, Birmingham, Ala. 35205.

November 27–30: Clinical Convention of the American Medical Association. Las Vegas, Nevada. Address: Dr. F. J. L. Blasingame, *Executive Vice President*, 535 North Dearborn Street, Chicago, Ill. 60610.

November 27–December 2: Radiological Society of North America. Palmer House, Chicago. Address: Dr. Maurice D. Frazer, *Secretary*, 5145 O Street, Lincoln, Neb. 68510.



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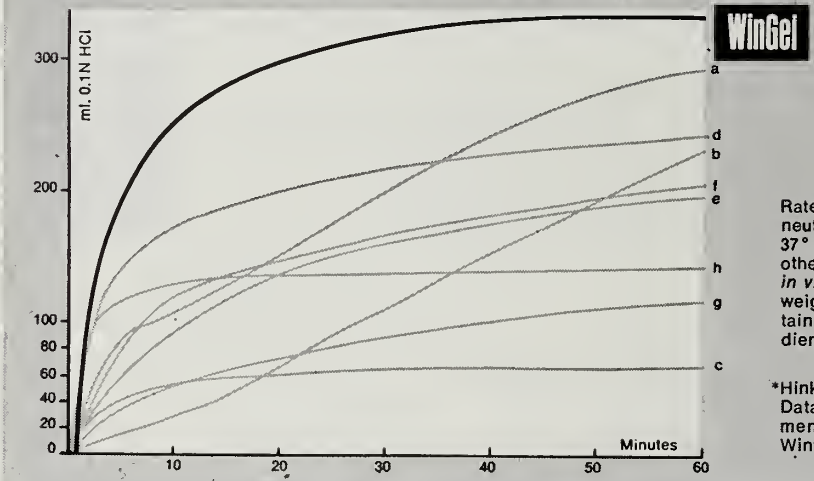

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*Hinkel, E. T., Jr. (New York): Data in the files of the Department of Medical Research, Winthrop Laboratories.

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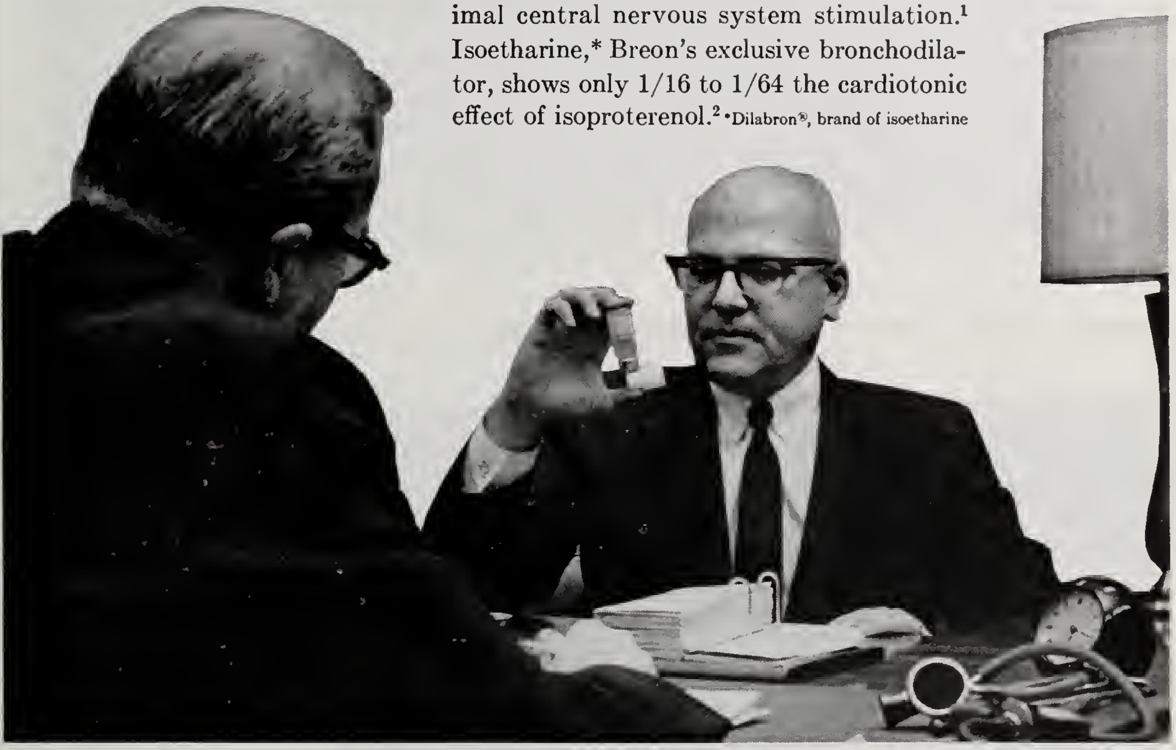

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COMPOSITION: Bronkometer delivers at the mouthpiece 200 metered doses of: 350 mcg isoetharine methanesulfonate (0.6%); 70 mcg phenylephrine HCl (0.125%); and 30 mcg thenyldiamine HCl (0.05%) with saccharin, menthol and fluorochlorohydrocarbons as inert propellants. Preserved with ascorbic acid 0.1% and alcohol 30%.

RECOMMENDED DOSAGE: One or two inhalations with at least one minute between inhalations. Occasionally more may be required, however in most cases, inhalations need not be repeated more than every four hours. Dosage should be adjusted to the severity of the condition and to patient's response.

PRECAUTIONS: Bronkometer is unusually free from cardiovascular and other side effects, but the usual precautions associated with sympathomimetic amines should be observed. Bronkometer should not be administered simultaneously with epinephrine or similar compounds because of the possibility of tachycardia, although it may be alternated with these agents. Dosage must be carefully adjusted in patients with hyperthyroidism, hypertension, acute coronary disease, cardiac asthma, limited cardiac reserve and in individuals sensitive to sympathomimetic amines.

SUPPLIED: 10 ml pressurized aerosol vials complete with measured dose valve and oral nebulizer.

References: 1. Spielman, A. D.: *Curr. Therap. Res.* 3:235 (June) 1961. 2. Herschfus, J. A.; Bresnick, E.; Levinson, L.; and Segal, M. S.: *Ann. Allergy* 9:769 (Nov.-Dec.) 1951.

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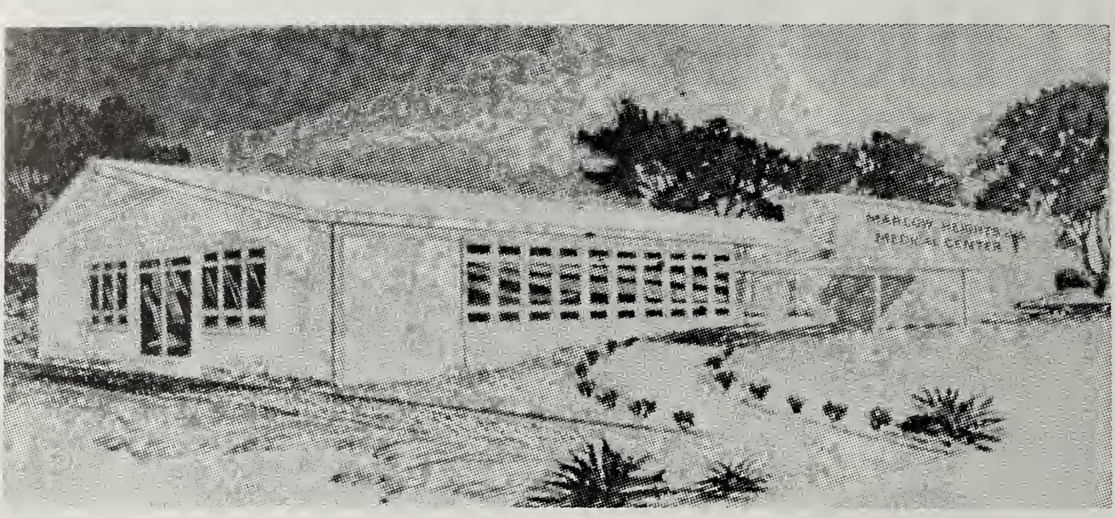
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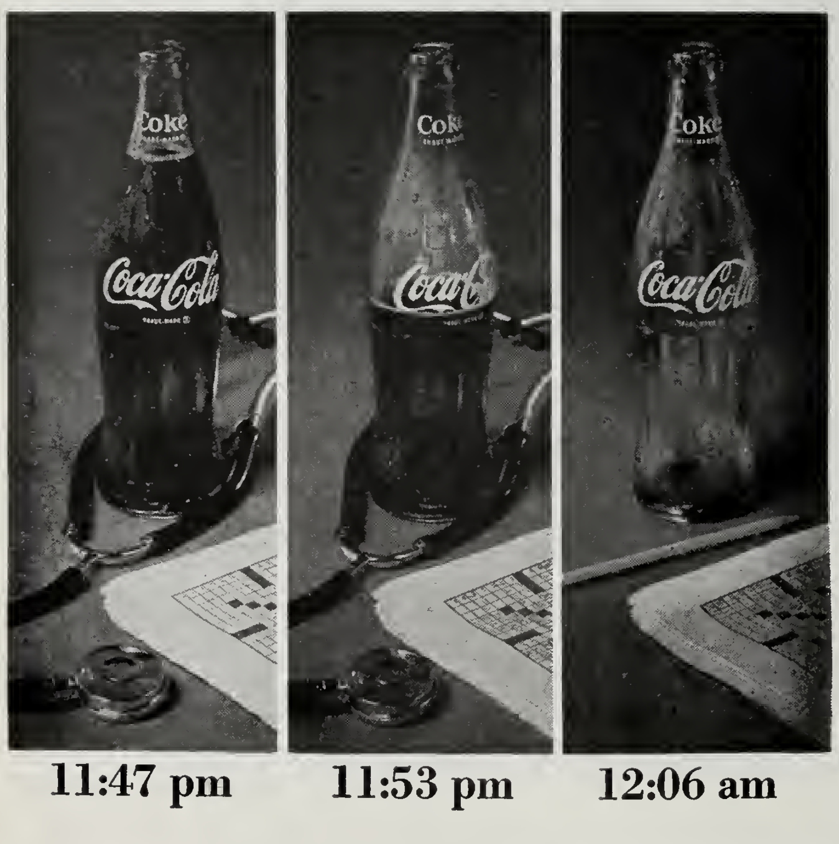
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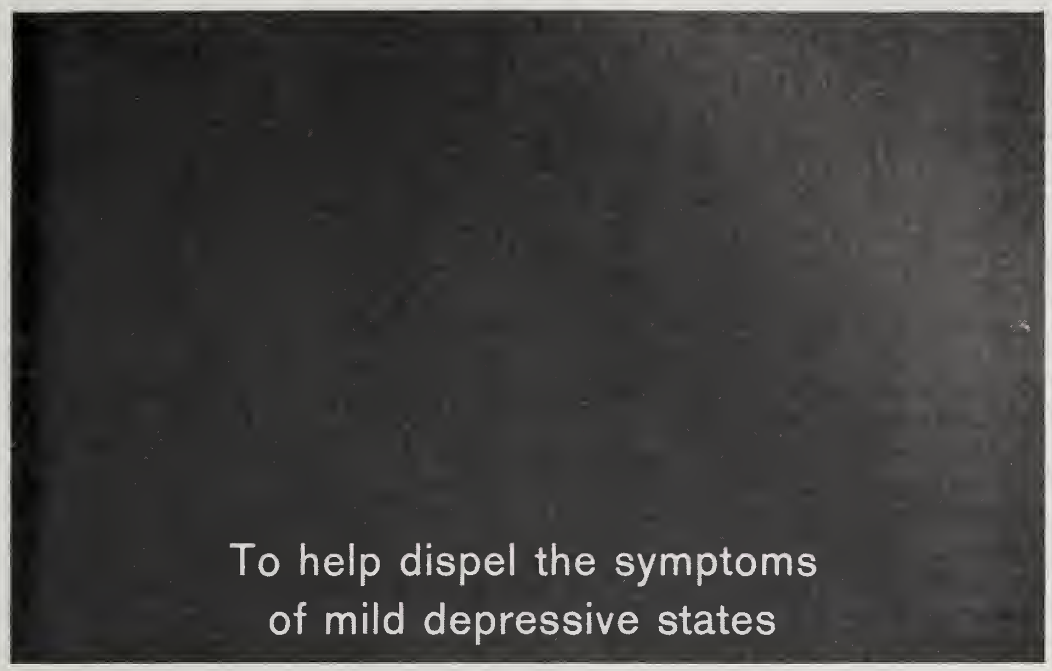

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The following is a brief precautionary statement. Before prescribing, the physician should be familiar with the complete prescribing information in SK&F literature or *PDR*.

Precautions: Use with caution in patients hypersensitive to sympathomimetics or barbiturates and in coronary or cardiovascular disease or severe hypertension. Do not use in patients taking MAO inhibitors. Excessive use of the amphetamines by unstable individuals may result in a psychological dependence; in these instances, withdraw the medication. Use cautiously in pregnant patients, especially in the first trimester. *Side effects:* Insomnia, excitability and increased motor activity are infrequent and ordinarily mild.

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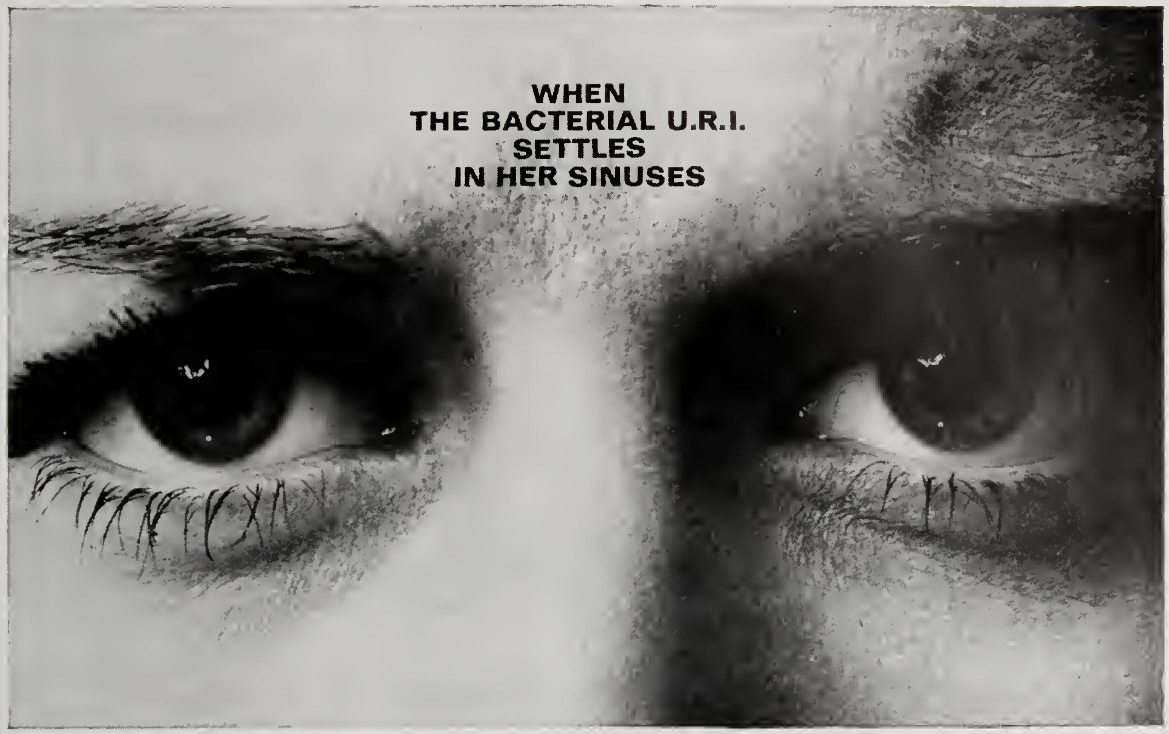

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Contraindication—History of hypersensitivity to tetracycline.

Warning—If renal impairment exists, even usual doses may lead to liver toxicity. Under such conditions, lower than usual doses are indicated and if therapy is prolonged, tetracycline serum level determination may be advisable. Hypersensitive individuals may develop a photodynamic reaction to natural or artificial sunlight during use. Individuals with a history of photosensitivity reactions should avoid direct exposure while under treatment and treatment should be discontinued at first evidence of skin discomfort.

Precautions—Some individuals may experience drowsiness, anorexia, and slight gastric distress. If excessive drowsiness occurs, it may be necessary to increase the interval between doses. Persons on full dosage should not operate any vehicle. Use may result in overgrowth of nonsusceptible organisms. If infections appear during therapy, appropriate measures should be taken. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Infections caused by beta-hemolytic streptococci should be treated for at least 10 full days to help prevent rheumatic fever or acute glomerulonephritis. Use of tetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect has been observed in usual short treatment courses.

Average adult dosage: 2 tablets four times daily, given at least one hour before, or two hours after meals.

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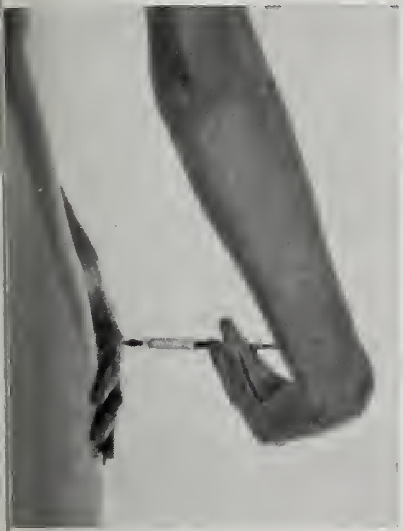
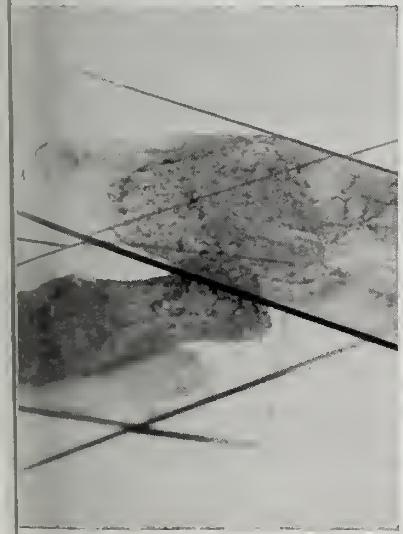


2. nonpregnant women with a history of recent or recurrent monilial vaginitis

3. elderly or debilitated patients

tients with a past history of moniliasis



5. patients on long-term tetracycline or corticosteroid therapy

BRISTOL THERAPEUTIC SUMMARY: For complete information consult Official Package Circular. *Indications:* Infections of respiratory, gastrointestinal and genitourinary tracts and skin and soft tissues due to tetracycline-sensitive organisms, in patients with increased susceptibility to monilial infections. *Contraindications:* The drug is contraindicated in patients hypersensitive to its components. *Warnings:* Photodynamic reactions have been produced by tetracyclines. Natural and artificial sunlight should be avoided during therapy. Stop treatment if skin discomfort occurs. With renal impairment, systemic accumulation and hepatotoxicity may occur. In this situation, lower doses should be used. Tooth staining and enamel hypoplasia may be induced during tooth development (last trimester of pregnancy, neonatal period and childhood). *Precautions:* Bacterial superinfection may occur. Infants may develop increased intracranial pressure with bulging fontanels. In gonorrheal therapy, serologic tests for syphilis should be conducted initially and monthly for 3 months. *Adverse Reactions:* Glossitis, stomatitis, nausea, diarrhea, flatulence, proctitis, vaginitis, dermatitis, and allergic reactions may occur. *Usual Adult Dosage:* 1 capsule *q.i.d.* Continue therapy for 10 days in beta-hemolytic streptococcal infections. Administer one hour before or 2 hours after meals. *Supply:* Capsules, bottles of 16. Each capsule contains tetracycline phosphate complex equivalent to 250 mg. tetracycline HCl activity and 250,000 units of nystatin.

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SQUIBB NOTES ON THERAPY

MOLECULAR REMODELING–

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis—a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect—metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors—in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'—an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase—it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic—an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9,10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

Naturetin—effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.

Contraindications: Severe renal impairment; previous hypersensitivity.

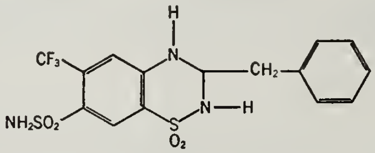
Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

References: **1.** Southworth, H.: Proc. Soc. Exper. Biol. & Med. *36*:58, 1937. **2.** Mann, T. and Keilin, D.: Nature *146*:164, 1940. **3.** Pitts, R. F., and Alexander, R. S.: Am. J. Physiol. *144*:239, 1945. **4.** Schwartz, W. B.: New England J. Med. *240*:173, 1949. **5.** Friedberg, C. K., in Moyer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia, W. B. Saunders Co., 1960, p. 259. **6.** Cumming, J. R.; Tabachnick, E., and Seelig, M., in Moyer, J. H., and Fuchs, M.: op. cit., p. 254. **7.** Werko, L., in Moyer, J. H., and Fuchs, M.: op. cit., p. 188. **8.** Beyer, K. H., Jr., in Moyer, J. H., and Fuchs, M.: op. cit., p. 274. **9.** Maren, T. H., and Wiley, C. E.: J. Pharmacol. & Exper. Therap. *143*:230, 1964. **10.** Earley, L. E., and Orloff, J.: Ann. Rev. Med. *15*:149, 1964. **11.** Fuchs, M., and Mallin, S. R., in Moyer, J. H., and Fuchs, M.: op. cit., p. 276. **12.** Ford, R. V., in Moyer, J. H., and Fuchs, M.: op. cit., p. 290. **13.** cited in Fuchs, M., and Mallin, S. R. (ref. 11): op. cit., p. 283.



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CONSIDER: an exceptionally high cure rate in susceptible infections

The rationale: When combined, Erythrocin and the trisulfapyrimidines (triple sulfas) are indicated in infections that are more susceptible to the combination than to either agent alone. Such conditions are usually found in urinary, lower respiratory tract and chronic ear conditions.

The results: Clinical studies involving 142 young patients showed *an overall cure rate of 96.5%*. Side effects were experienced by only four of the patients.

The acceptance: The majority of the 142 patients studied expressed a definite liking for the products. *There were only two refusals.* An independent taste-test with 50 healthy children further substantiated the excellent acceptability of the orange-flavored forms.

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Brief Summary

Indications: Use Erythrocin-Sulfas in infections more susceptible to the combination than to either agent alone. These are usually found in urinary, lower respiratory tract, and chronic ear infections.

Contraindications: Known sensitivity to erythromycin or sulfonamides. Because of the possibility of kernicterus with sulfonamides, do not use in pregnancy at term, premature or new born infants.

Warnings: As with other forms of sulfonamide therapy, carefully evaluate patients with liver or kidney damage, urinary obstruction, or blood dyscrasia. Deaths have been reported from hypersensitivity reactions and blood dyscrasias following use of sulfonamides. Perform blood counts and liver and kidney function tests if used repeatedly at close intervals or for long periods.

Precautions: Use sulfonamides with caution in patients with a history of allergy. Assure adequate fluid intake to prevent crystalluria and institute alkali therapy if indicated.

Adverse Reactions: Sulfonamide therapy may be associated with headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, injection of the conjunctiva and sclera, petechiae, purpura, hematuria and crystalluria.

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BOOKS RECEIVED

Acknowledgment is made of the following books which have recently been received.

Resuscitation of the Newborn Infant and Related Emergency Procedures. Principles and Practice, 2nd ed. Edited by HAROLD ABRAMSON, A.M., M.D. Price, $16.50. Pp. 411, illustrated. St. Louis: Mosby, 1966.

Arteriography: Principles and Techniques. Emphasizing Its Application in Community Hospital Practice. JOSEPH L. CURRY, M.D., AND WILLARD J. HOWLAND, M.D. Price, $14.00. Pp. 328, with 223 illustrations. Philadelphia: Saunders, 1966.

Spontaneous Regression of Cancer. A Study and Abstract of Reports in the World Medical Literature and of Personal Communications Concerning Spontaneous Regression of Malignant Disease. TILDEN C. EVERSON, M.D., PH.D., F.A.C.S., AND WARREN H. COLE, M.D., F.A.C.S., F.R.C.S. (Eng., Hon.), F.R.C.S. (Edin., Hon.). Price, $20.00. Pp. 560, illustrated. Philadelphia: Saunders, 1966.

An Atlas of Fine Structure. The Cell. Its Organelles and Inclusions. DON W. FAWCETT, M.D. Price, $11.00. Pp. 448, with 240 figures. Philadelphia: Saunders, 1966.

Synopsis of Neurology, 2nd ed. FRANCIS M. FORSTER, B. S., M.D. Price, $7.50. Pp. 218. St. Louis: Mosby, 1966.

Diseases of the Heart, 3rd ed. CHARLES K. FRIEDBERG, M.D. Price, $22.00 single volume, $26.00 two-volume set. Pp. 1787, illustrated. Philadelphia: Saunders, 1966.

Emergency Care of the Sick and Injured. A Manual for Law-Enforcement Officers, Fire-Fighters, Ambulance Personnel, Rescue Squads and Nurses. By the Committee on Trauma, American College of Surgeons. Edited by ROBERT H. KENNEDY, M.D., F.A.C.S. Price (paper), $2.00. Pp. 128, illustrated. Philadelphia: Saunders, 1966.

The Pediatrician's Ophthalmology. A collaborative effort of several authors. Edited by SUMNER D. LIEBMAN, M.D., AND SYDNEY S. GELLIS, M.D. Price, $19.50. Pp. 352, with 120 text illustrations and 7 color plates. St. Louis: Mosby, 1966.

Miles to Go: Report of the Mental Retardation Planning Project, March 1966. Connecticut State Department of Health. ROBERT I. CATLIN, Chairman, Planning Project Advisory Committee. Pp. 314. Hartford, Conn.: Connecticut State Department of Health, 1966.

Operable Heart Disease. Pathophysiology, Diagnosis, and Treatment. HOWARD D. SIRAK, M.D. Price, $12.50. Pp. 130, with 36 illustrations. St. Louis: Mosby, 1966.

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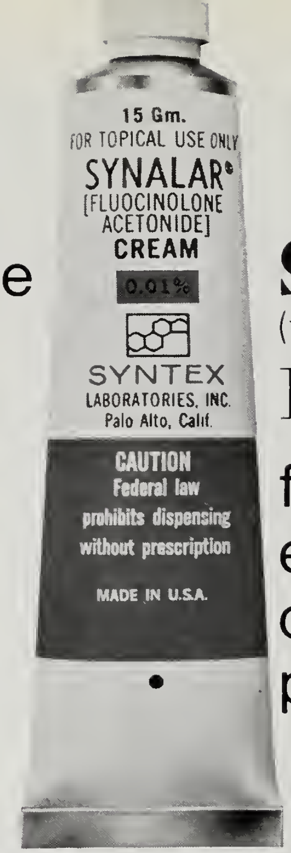

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Levy, E. J.: J New Drugs 1:262 (Nov.-Dec.) 1961. 2. Meenan, F. O.: J
Med Ass 52:75 (Mar.) 1963. 3. Robinson, H. M., Jr., Raskin, J., and Duns
W. J. R.: Southern Med J 56:797 (Jul.) 1963.

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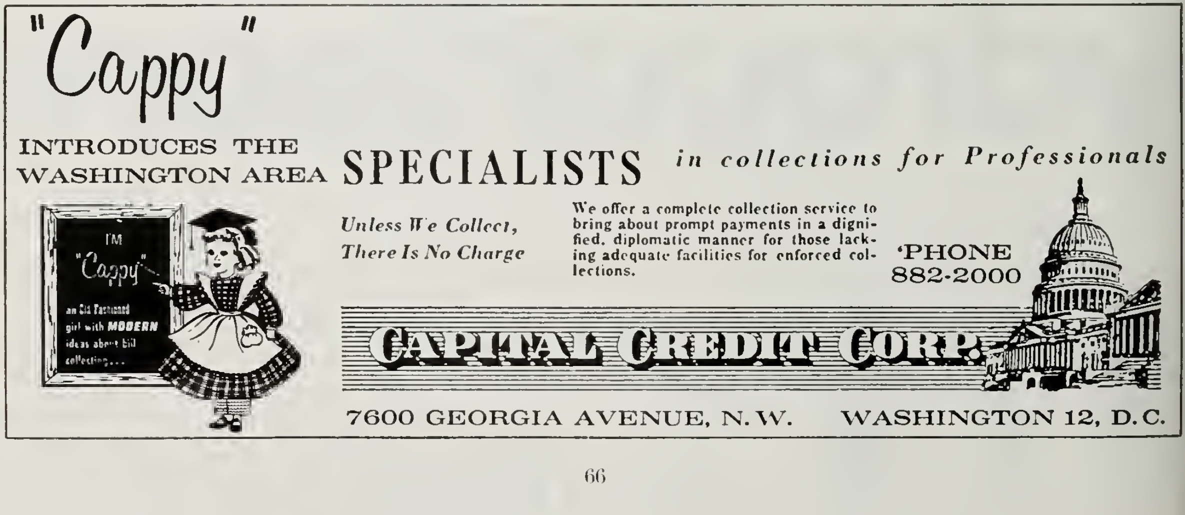
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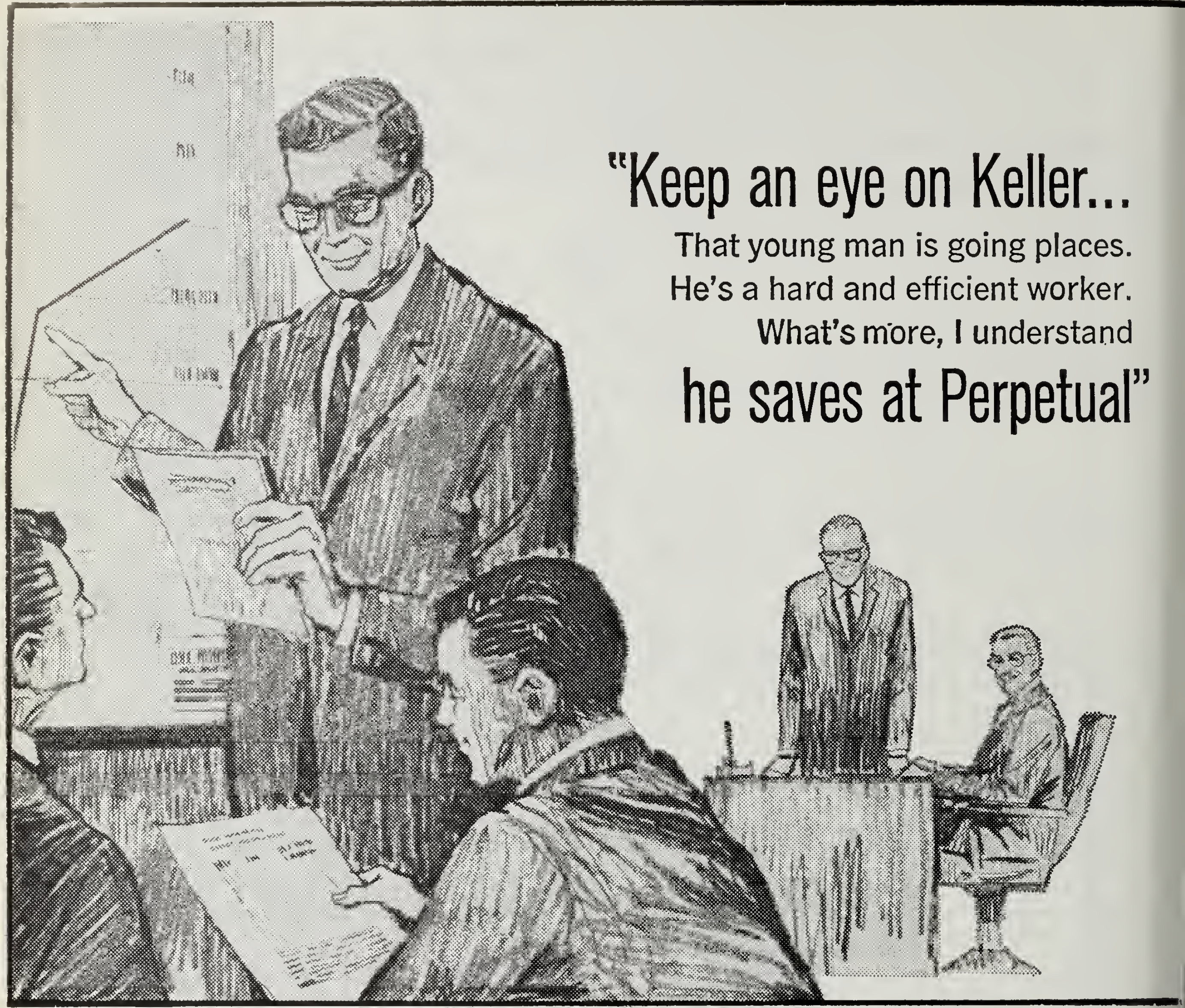
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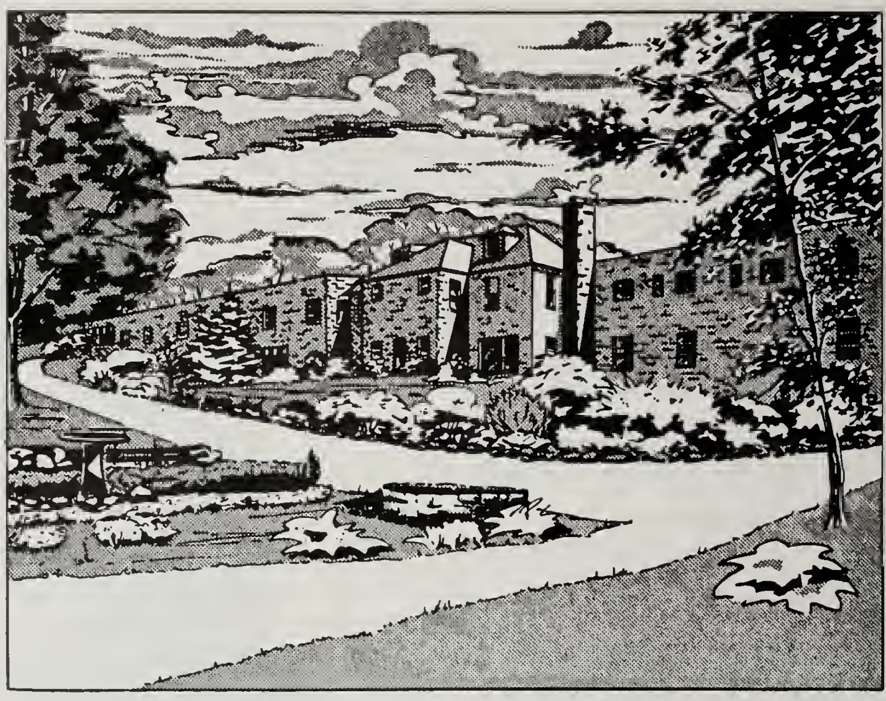

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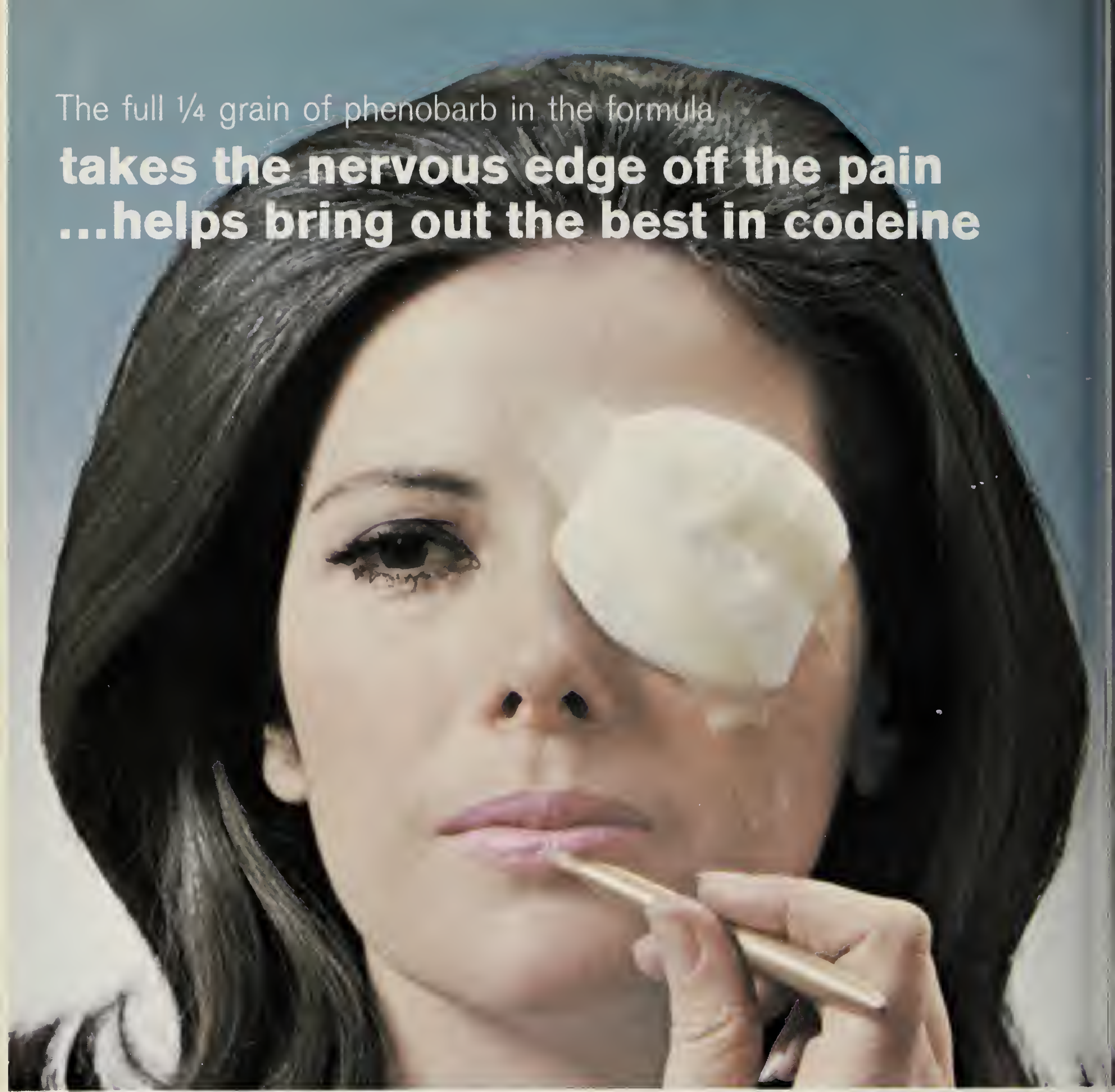
*Schiller, I. W., and Lowell, F. C.: New England J. Med. 261:478, 1959.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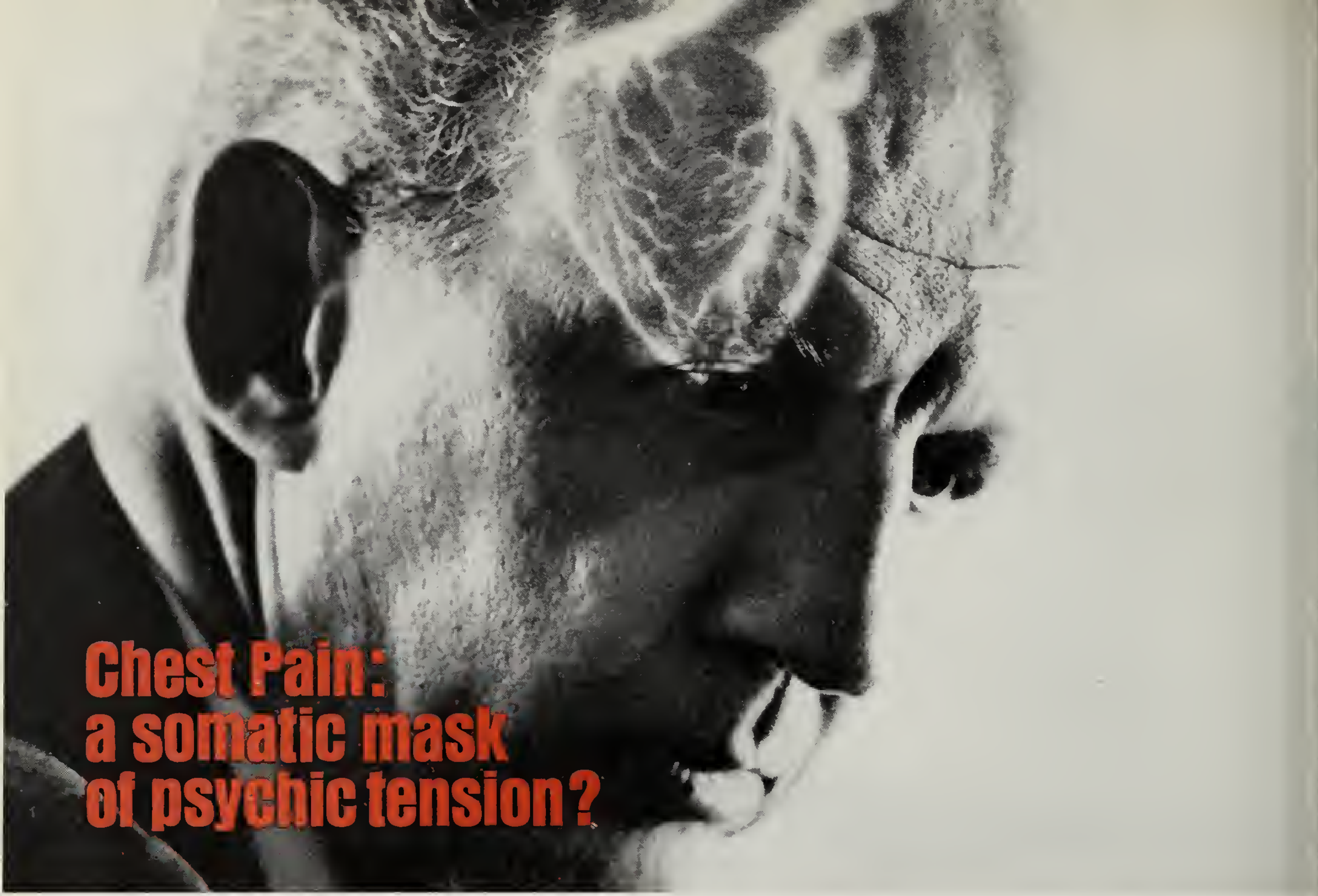

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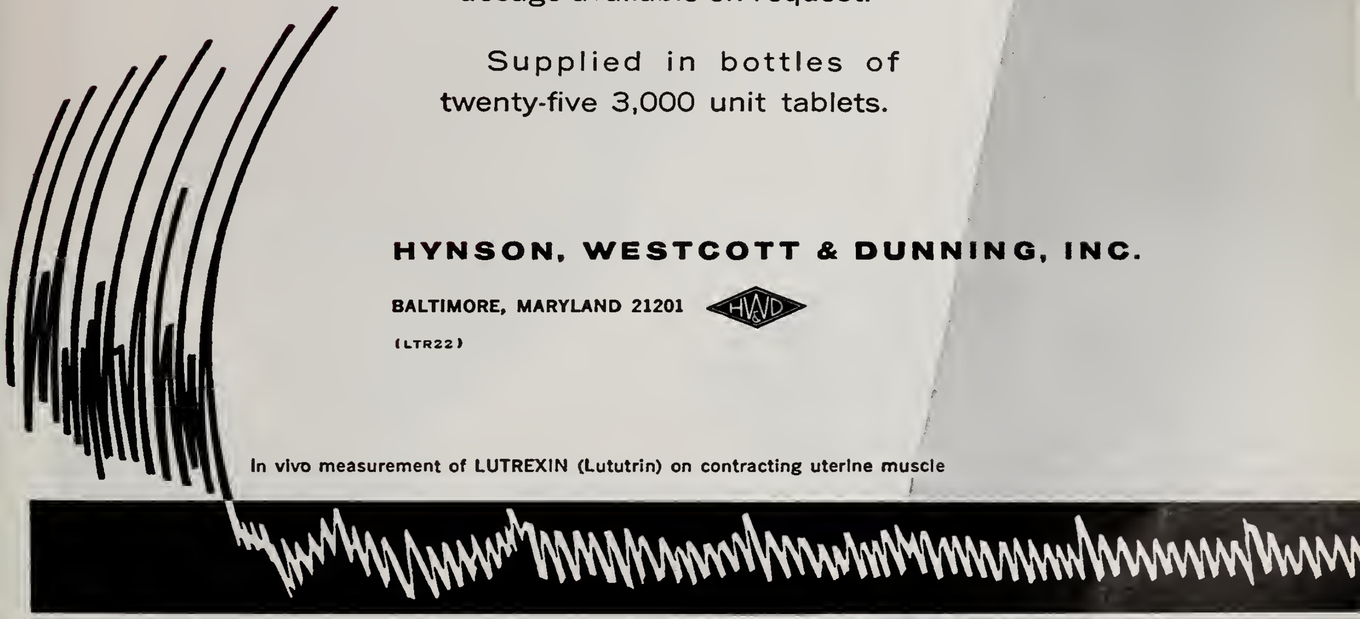

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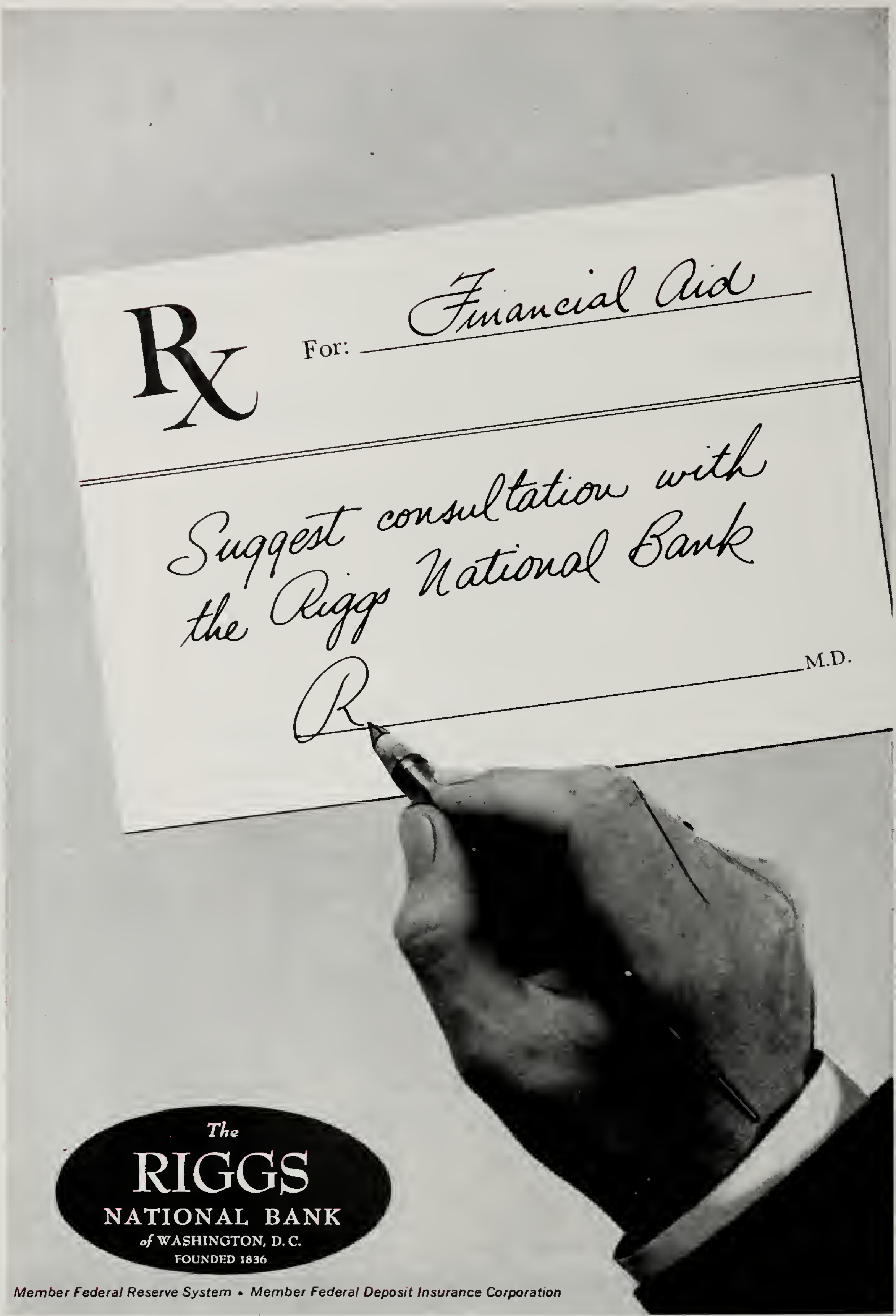
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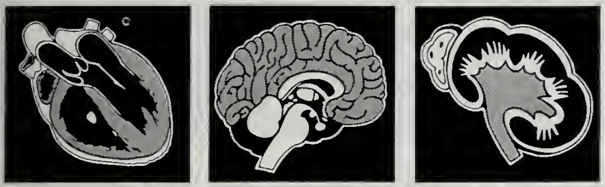
SQUIBB NOTES ON THERAPY

Behind continued high blood pressure readings lies the possibility of organic damage[1-13]

MANY OF THE aspects of essential hypertension are unpredictable—either because there are a number of mechanisms involved or because individuals differ in their responses to these mechanisms.[1]

There is one aspect of hypertension, however, that seems, in many cases, predictable. ". . . when the blood pressure is elevated to a marked degree for an adequate period of time, this in itself leads to perpetuation of the syndrome with resulting vascular damage throughout the body."[14] All too often the disease progresses until there is damage to one of three vital organs: the heart, the kidney, the brain.



> "Hypertension is certainly a major factor in the genesis of coronary heart disease, and it is even more important when compounded with obesity."[4]
>
> "[Vascular deterioration] can be clearly seen in the kidney with a degree of damage that can be measured by renal function studies."[10]

". . . most evidence suggests that reduction of blood pressure, when it is too high, not only relieves the heart of excess work but reduces vascular damage."[1]

"In short, treatment is indicated."[1]

Antihypertensive therapy will not restore the blood vessels to normal. Yet many of the vascular changes and symptoms caused by increased blood pressure may be arrested or alleviated when the blood pressure is reduced to normotensive levels.[7]

Reducing the blood pressure helps curtail further vascular damage and improves the prognosis — when damage is not too far advanced before therapy is started.[14] Essential hypertension is an indication not only for treatment, but for *early* and adequate treatment of the patient in question.

Reduce the blood pressure with Rautrax-N

Rautrax-N combines the antihypertensive-tranquilizing action of whole root rauwolfia with the antihypertensive-diuretic action of bendroflumethiazide in one convenient medication. The two drugs complement each other so that smaller doses of both are possible.

Rauwolfia combined with bendroflumethiazide is particularly effective in long-term therapy,[15-17] since beneficial effects do not diminish with continuous daily administration.

For most patients 1 or 2 Rautrax-N tablets daily are sufficient for maintenance therapy. The simplicity, convenience and economy of such a dosage schedule are of particular benefit to older patients.

References: 1. Page, I. H., and Dustan, H. P.: The Usefulness of Drugs in the Treatment of Hypertension, in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 95. **2.** Hollander, W.: The Evaluation of Antihypertensive Therapy of Essential Hypertension in Ingelfinger, F. J.; Relman, A. S., and Finland, M.: Controversy in Internal Medicine, Philadelphia, W. B. Saunders Co., 1966, p. 97. **3.** Nickerson, M.: Antihypertensive Agents and the Drug Therapy of Hypertension, in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Co., 1965, p. 727. **4.** Berkson, D. M.: Indust. Med. & Surg. **32**:371, 1963. **5.** Cohen, B. M.: M. Times **91**:645, 1963. **6.** Lee, R. E., et al.: Am. J. Cardiol. **11**:738, 1963. **7.** Moyer, J. H.: Am. J. Cardiol. **9**:821, 1962. **8.** Moser, M.: New York J. Med. **62**:1177, 1962. **9.** Wood, J. E., and Battey, L. L.: Am. J. Cardiol. **9**:675, 1962. **10.** Moyer, J. H., and Heider, C.: Am. J. Cardiol. **9**:920, 1962. **11.** Moser, M., and Macaulay, A. I.: New York State J. Med. **60**:2679, 1960. **12.** Judson, W. E.: Nebraska M. J. **44**:305, 1959. **13.** Hodge, J. V.; McQueen, E. G., and Smirk, H.: Brit. M. J. **1**:5218, 1961. **14.** Moyer, J. H., and Brest, A. N.: Hypertension Recent Advances, Philadelphia, Lea & Febiger, 1961, p. 633. **15.** Berry, R. L., and Bray, H. P.: J. Am. Geriatrics Soc. **10**:516, 1962. **16.** Reid, W. J.: J. Am. Geriatrics Soc. **13**:365, 1965. **17.** Feldman, L. H.: North Carolina M. J. **23**:248, 1962.

Contraindications: Severe renal impairment or previous hypersensitivity. **Warning:** Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting or G.I. bleeding occur.

Precautions and Side Effects: The dose of ganglionic blocking agents, veratrum or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Caution is indicated in patients with depression, suicidal tendencies, peptic ulcer; electrolyte disturbances are possible in cirrhotic or digitalized patients. Marked hypotension during surgery is possible; consider discontinuing two weeks prior to elective surgery and observe patients closely during emergency surgery. Rauwolfia preparations may cause reversible extrapyramidal symptoms and emotional depression, diarrhea, weight gain, edema, drowsiness may occur. Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients, and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, rashes may occur.

Dosage and Supply: Initial dosage, 1 to 4 tablets daily, preferably at mealtime. Maintenance, 1 or 2 tablets daily. Rautrax-N is supplied as capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin®), 4 mg. bendroflumethiazide (Naturetin®), 400 mg. potassium chloride.

Also available: Rautrax-N Modified — capsule-shaped tablets containing 50 mg. Rauwolfia serpentina whole root (Raudixin), 2 mg. bendroflumethiazide (Naturetin), 400 mg. potassium chloride. Both potencies available in bottles of 100. For full information, see Product Brief.

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Contraindications
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Warning
If coumarin-type anticoagulants are given simultaneously, the physician should watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Patients receiving such concomitant therapy should be carefully observed for this effect.

Use with caution in the first trimester of pregnancy.

Precautions
Before prescribing, the physician should obtain a detailed history and perform a complete physical and laboratory examination, including a blood count. The patient should be kept under close supervision and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools. Regular blood counts should be made to guard against blood dyscrasias.

Adverse Reactions
The most common adverse reactions are nausea, edema and drug rash. Moderately lowered red cell count may sometimes occur due to hemodilution. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vertigo or languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia are also possible side effects.

Confusional states, hyperglycemia, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hepatitis, jaundice and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently.

Dosage
The initial daily dosage in adults is 300-600 mg. daily in divided doses. In most instances, 400 mg. daily is sufficient. When improvement occurs, dosage should be decreased to the minimum effective level: this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

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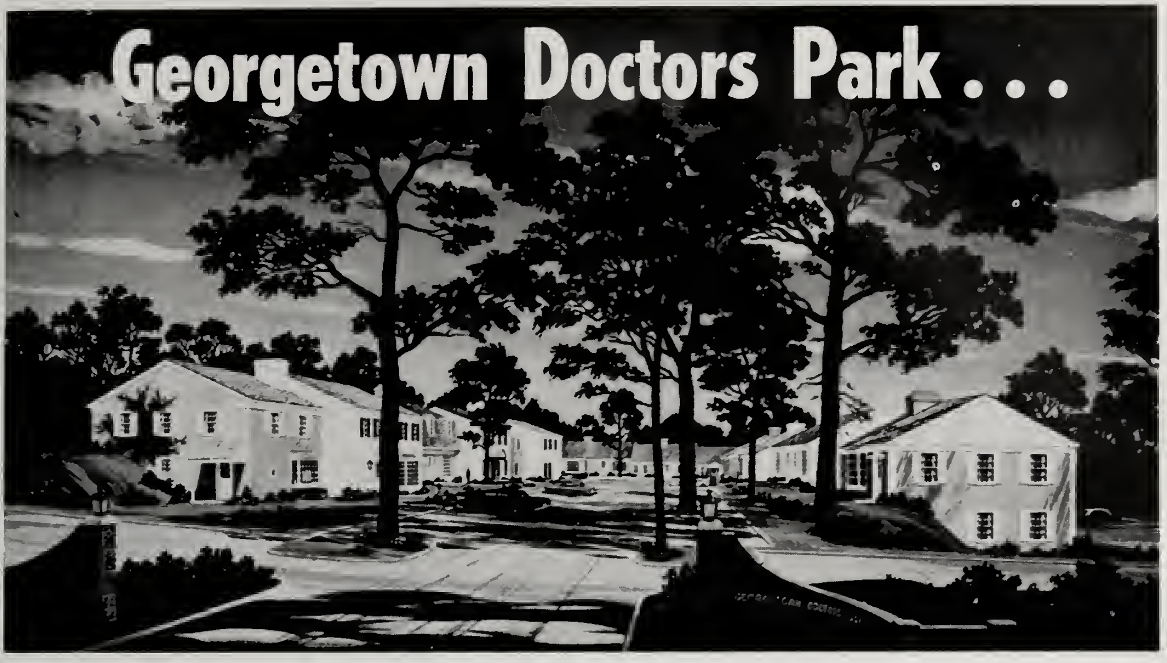

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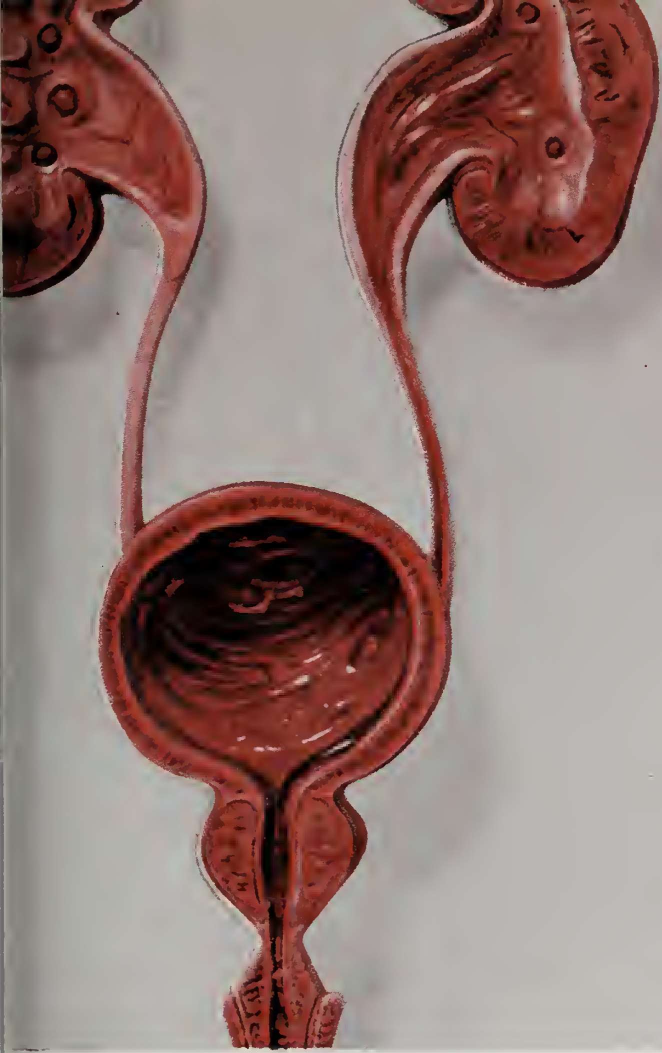

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sitive organisms.

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sinophilia, reversible subjective visual disturbances (overbrightness of
hts, change in visual color perception, difficulty in focusing, decrease in
ual acuity and double vision), and reversible photosensitivity reactions.
rked overdosage, coupled with certain predisposing factors, has produced
ef convulsions in a few patients.

cautions: As with all new drugs, blood and liver function tests are advis-
e during prolonged treatment. **Pending further experience, like most
emotherapeutic agents, this drug should not be given in the first trimester
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ttles of 1000. **250 mg. for children,** available in bottles of 56 and 1000.

ferences: (1) Based on 23 clinical papers, 1512 cases. Bibliography on
quest. (2) Bush, I. M., Orkin, L. A., and Winter, J. W., in Sylvester, J. C.:
timicrobial Agents and Chemotherapy — 1964, Ann Arbor, American
ciety for Microbiology, 1965, p. 722.

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*Multiple of adult Minimum Daily Requirement supplied.
†The need for these substances in human nutrition has not been established.

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Dosage: Adults, 1 tablespoonful; children (over 15 years old), 1 to 2 teaspoonfuls; children (4 to 15 years old), 1 teaspoonful. To be taken three times daily 30 minutes before meals.

Contraindications: As with other drugs with CNS stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive compulsive states.

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vignettes of angina pectoris—
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angina and the surgeon

John Hunter—
British surgeon (1728-1793)

angina of anger

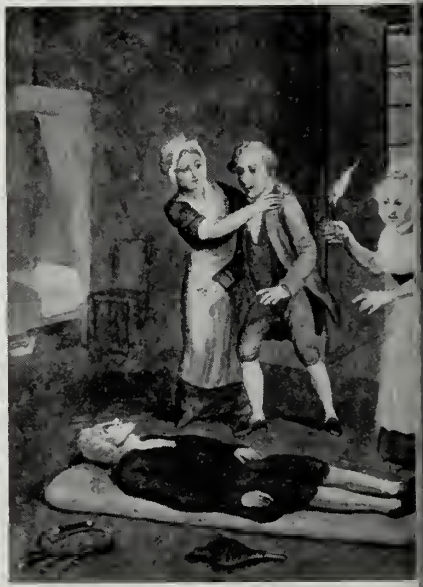
“My life is in the hands of any rascal who chooses to annoy and tease me.”[1] So said the great British surgeon and anatomist, John Hunter, realizing that he could not control the anger which precipitated frequent and severe attacks of angina pectoris. According to Mettler: “His statement was no exaggeration. On October 16, 1793, he attended a meeting of the St. George’s hospital staff, and, while defending the interests of several students, he was contradicted and thoroughly antagonized. The pains of angina commenced, he started toward another room, gained it, and fell dying into the arms of a physician.”[2]

Why Edward Jenner withheld his paper on angina In 1777, at an earlier stage of the condition, Hunter’s angina alarmed a favorite pupil, Edward Jenner, who wrote to Dr. Heberden that he feared his teacher was “affected with symptoms of the Angina Pectoris.”[3] So concerned was Jenner about his former teacher’s emotion-related condition that he deliberately cancelled publication of a paper on angina pectoris, fearing that Hunter would read it, and have “his fears excited by its truly formidable nature.”[4]

Severity of angina described Hunter’s brother-in-law, Dr. Everard Home, who witnessed his death and performed an autopsy, gave this account of the later stage of the condition:

“. . . the pain became excruciating at the apex of the heart; the throa was so sore as not to allow of an attempt to swallow anything and the left arm could not bear to be touched. . . .

“The affections above described were, in the beginning, readily brought on by exercise . . . but they at last seized him when lying in bed, and in his sleep. . . .”[5]



18th century ancestor of the modern coronary candidate Surgeon, anatomist, pathologist, physiologist, geologist, and teacher Hunter had a passion for research which led him to disregard his practice, his health and even the

w. When the Irish giant O'Brien
arned that Hunter desired his
keleton for a museum, he willed
hat his body be sunk at sea in a
ad coffin. But Hunter was not to
e denied. According to Major, he
. . . bribed the watchers and finally
btained the body at a cost of 500
ounds although he had to borrow
e money to pay the men."[3]
1767, he experimentally inocu-
ted himself with gonorrhea and
philis, treated himself with
ercury for three years, and was
pparently cured.[5] Hunter had
elings of inadequacy about his
ducation and speaking ability,
ut this did not prevent him from
eing hard driving and abrupt
ith his colleagues. His competi-
veness with his physician older
rother was also well known, and
nded in complete estrangement
etween the two men.[2,3] Today, the
ersonality traits seen in John
unter are recognized to be impor-
nt predisposing factors in the devel-
pment of coronary artery disease—
ften manifested as angina pectoris.
ccording to Friedman and Rosen-
an,[6] in a group of men whose be-
avior was characterized by intense
nbition and competitive drive,
greater than average incidence
angina pectoris was among those
normal conditions noted.

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in the modern management of angina pectoris

Peritrate® SA

Sustained Action (pentaerythritol tetranitrate) 80 mg.

Each double-layer, biconvex, dark green/light green tablet of Peritrate SA Sustained Action contains:
pentaerythritol tetranitrate . . . . 80 mg.
(20 mg. in immediate release layer and 60 mg. in sustained release base)

Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Actions: The exact cause of angina pectoris (that is, the pain associated with coronary artery disease) remains obscure, despite the numerous and often conflicting hypotheses concerning its pathophysiology. Therapy at the present time, therefore, remains essentially empiric. Customarily, clinical improvement has been measured by: reduction in (1) number, intensity and duration of angina pectoris attacks and (2) necessity for glyceryl trinitrate intake for prevention or relief of anginal attacks.

Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. has been reported in clinical usage to reduce in number and severity the incidence of angina pectoris attacks, with concomitant reduction in glyceryl trinitrate intake.

In the evaluation of Peritrate (pentaerythritol tetranitrate) and Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. in angina pectoris, clinical improvement has been customarily measured subjectively by reduction in number and severity of attacks and necessity for glyceryl trinitrate intake for prevention or abortion of anginal attacks. Individual patterns of angina pectoris differ widely as does the symptomatic response to antianginal agents such as pentaerythritol tetranitrate. The published literature contains both favorable and unfavorable clinical reports. In conjunction with total management of the patient with angina pectoris, Peritrate (pentaerythritol tetranitrate) and Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. have been accepted as safe for prolonged administration and widely regarded as useful.

Animal pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artificially induced occlusion of a major artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Pigs rather than dogs were used because their coronary artery distribution more closely resembles that of human beings. Studies in dogs subject to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to human behavior

Indications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg. is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Should be used with caution in patients who have glaucoma.

Adverse reactions: Side effects reported to date have been predominantly related to headache (which may require discontinuation of medication) and gastrointestinal distress which are usually transient with continuation of medication.

Dosage: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg., 1 tablet immediately on arising and 1 tablet 12 hours later (on an empty stomach).

Additional dosage forms
Peritrate (pentaerythritol tetranitrate)—10 mg. and 20 mg. tablets with or without phenobarbital.

Peritrate with Phenobarbital SA Sustained Action—80 mg. pentaerythritol tetranitrate and 45 mg. phenobarbital.

(**Warning:** Tablets containing phenobarbital may be habit forming.)

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Morris Plains, N. J.

postoperative atelectasis of remaining right lung after pneumonectomy*

To clear the airway in bronchopulmonary disease–Dornavac® (pancreatic dornase)

Only Dornavac—the pancreatic enzyme for inhalation therapy—offers:

- selective action against DNA-protein complex—a major contributor to the viscosity of purulent secretions
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- wide margin of safety—attested by years of extensive clinical use
- compatibility with IPPB and other equipment

Successful in removing thick mucus and pus even in far-advanced bronchopulmonary diseases[1]

"A broad spectrum of chronic bronchopulmonary disease has been treated with this enzyme [Dornavac] and it has been found useful in patients with pulmonary disease complicated by thick secretions or thick pus, such as bronchiectasis or lung abscess. It has proved to be of real value in patients with chronic debilitating diseases who develop pulmonary complications and have difficulty in raising sputum. In these cases, as with postoperative patients, it has been lifesaving."[2]

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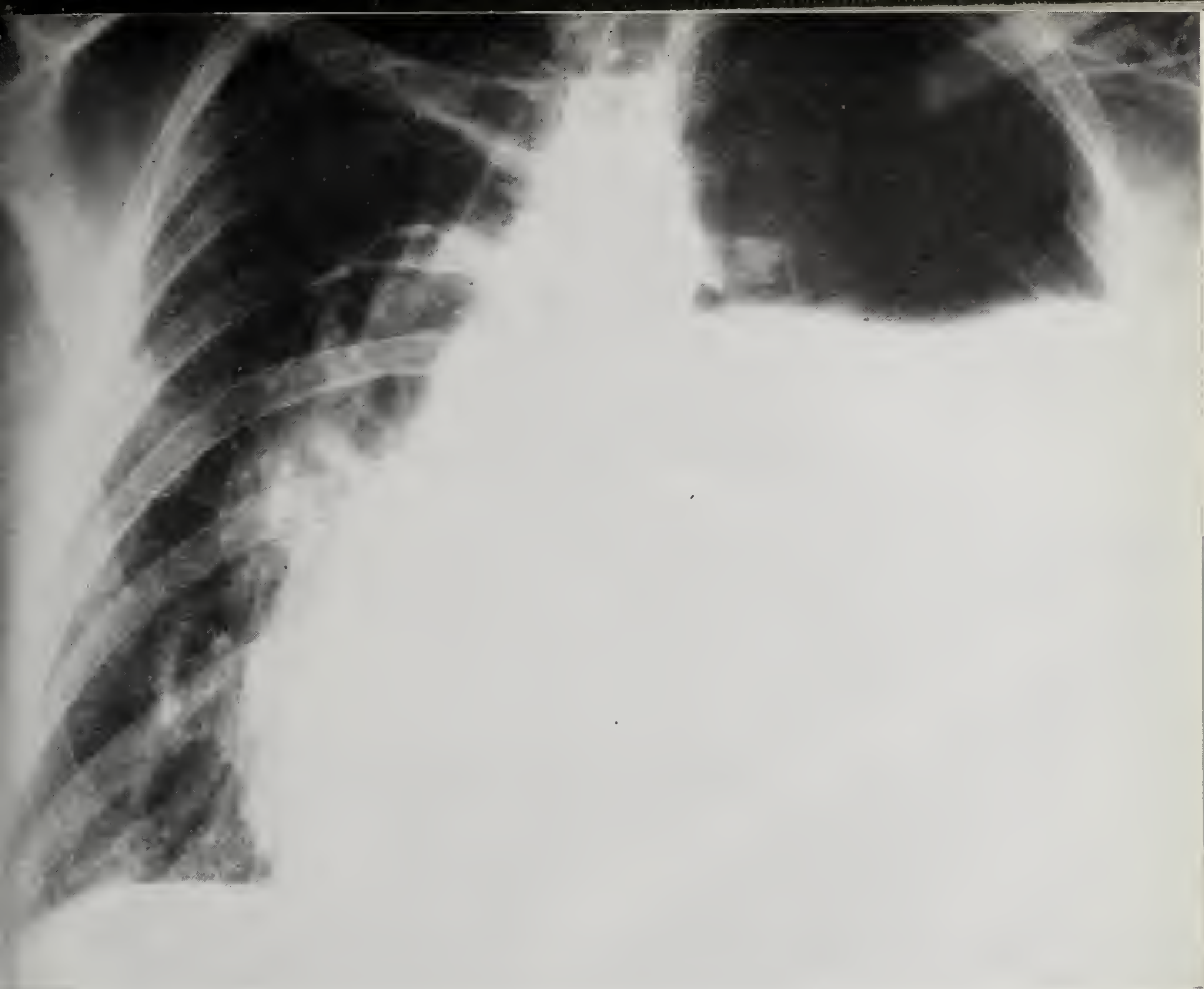

complete reexpansion of remaining right lung after three days of treatment with DORNAVAC® (pancreatic dornase)*

degrades and thins thick, adherent, mucopurulent secretions on contact.

References: 1. Cliffton, E. E.: Dis. Chest 30:373, Oct., 1956. 2. Cliffton, E. E., and Grossi, C. E.: Cancer *14*:414, Mar.-April, 1961.

Indications: For lysing purulent exudates in bronchopulmonary infections, paranasal sinus infections, tracheitis sicca, cystic fibrosis of the pancreas, and purulent urologic conditions. Aerosolized DORNAVAC may be a useful adjunct to obtain a specimen of bronchial secretions and cellular debris for cytologic study in suspected bronchogenic carcinoma.

Precautions: Rare anaphylactoid type reactions have occurred. Consider possibility of hypersensitivity, particularly in those sensitive to beef protein. Occasional pharyngeal irritation. Do not administer parenterally. Reconstitute just before application and use immediately to assure maximum potency.

Before prescribing or administering, read product circular with package or available on request.

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A key agent in the total therapeutic regimen for mucopurulent bronchopulmonary conditions

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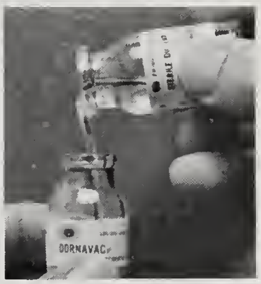

Since there is no vacuum, a *needle and syringe are not needed* unless aseptic reconstitution is desired. Convenient tear-down tabs and wide-mouth vials make it easy to pour diluent into the vial containing DORNAVAC.

*Roentgenograms courtesy of E. E. Cliffton, M.D., and C. E. Grossi, M.D.: Amer. J. Surg. *100*:447, Sept., 1960.

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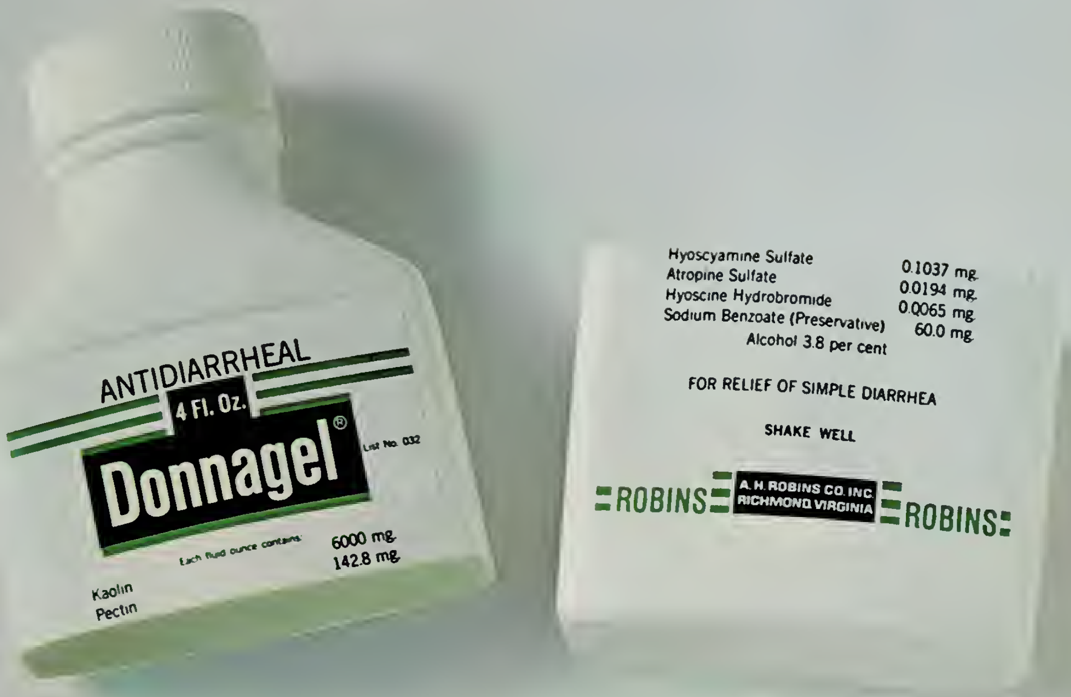
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Pectin exerts its demulcent effect in the entire tract and its detoxifying action primarily in the large bowel to diminish irritation of the mucosa and help restore normal intestinal flora and function.

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References: 1. Kramer, P., and Ingelfinger, F.J.: Med. Clin. N. Amer., *32*:1227, 1948. 2. Hock, C.W.: Clin. Med., *8*:1932, 1961. 3. Winfield, I.W.: Am. J. Gastroent., *31*:438, 1959.

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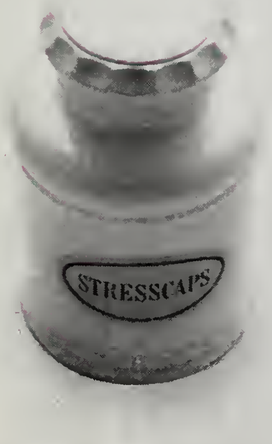

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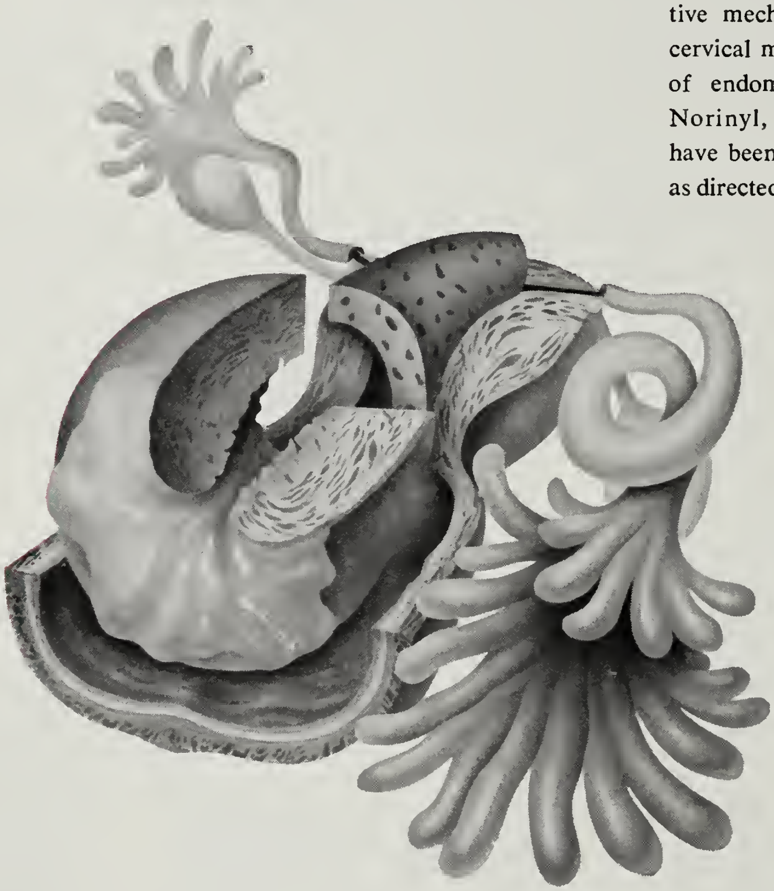
Norinyl provides multiple action for maximum assurance of success. It does not depend on ovulation inhibition alone for contraceptive effectiveness. The mechanism of action of combined hormonal therapy results in ovulation inhibition reinforced by other protective mechanisms, including a hostile cervical mucus[1-13] and an acceleration of endometrial changes.[1-3,7-16] With Norinyl, no unplanned pregnancies have been reported to date when used as directed.



plus important supportive benefits that help her through those critical early months of oral contraception

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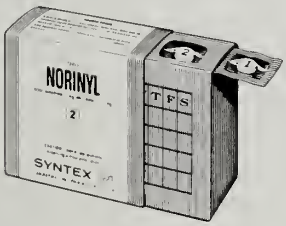

Contraindications: Thrombophlebitis or pulmonary embolism (current or past). Existing evidence does not support a causal relationship between use of Norinyl and development of thromboembolism. While a study which was conducted does not resolve definitively the possible etiologic relationship between progestational agents and intravascular clotting, it tends to confirm the findings of the Ad Hoc Advisory Committee appointed by the Food and Drug Administration to review this possibility. Cardiac, renal or hepatic dysfunction. Carcinoma of the breast or genital tract. Patients with a history of psychic depression should be carefully studied and the drug discontinued if depression recurs to marked degree. Patients with a history of cerebral vascular accident.

Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: **1.** Council on Drugs. JAMA 187:664 (Feb. 29) 1964. **2.** Bryans, F. E.: Canad Med Ass J 92:287 (Feb. 6) 1965. **3.** Goldzieher, J. W.: Med Clin N Amer 48:529 (Mar.) 1964 **4.** Cohen, M. R: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965. **5.** Hammond, D. O.: Ibid. **6.** Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A: Fertil Steril 14:402 (Jul.-Aug.) 1963. **7.** Goldzieher, J. W., Moses, L. E., and Ellis, L. T.: JAMA 180:359 (May 5) 1962 **8.** Kempers, R. D.: GP 29:88 (Jan.) 1964 **9.** Tyler, E. T.: JAMA 187:562 (Feb. 22) 1964. **10.** Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M Fertil Steril 16:158 (Mar.-Apr.) 1965. **11.** Flowers, C E., Jr: N Carolina Med J 25:139 (Apr.) 1964 **12.** Goldzieher, J. W.: Appl Ther 6:503 (June) 1964 **13.** The Control of Fertility Report adopted by the Committee on Human Reproduction of the American Medical Association. JAMA 194:462 (Oct. 25) 1965. **14.** Flowers, C. E., Jr: JAMA 188:1115 (June 29) 1964. **15.** Merritt, R. I.: Appl Ther 6:427 (May) 1964. **16.** Newland, D. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

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This clinical study shows that the two combinations of antibiotics were not superior to some of their single components. The authors point out that antibiotic antagonism often negates theoretical advantages of multiple therapy. Coly-Mycin Injectable (colistimethate sodium) was one of the single components that was shown to be equal to the combinations and eradicated bacteriuria in two-thirds of the patients.

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[1] McCabe, W. R., and Jackson, G. G.: New England J. Med. *272*:1037, 1965.

in gram-negative urinary tract infections often the single well-chosen agent

COLY-MYCIN
INJECTABLE

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Indications: Especially indicated for the treatment of severe acute and resistant chronic urinary tract infections due to sensitive strains of gram-negative organisms. Also indicated in respiratory tract, surgical, wound and burn infections and in septicemia due to sensitive organisms. Particularly indicated when any of these infections are caused by sensitive strains of *Pseudomonas aeruginosa*.

Adverse Reactions: Occasional reactions such as circumoral paresthesias, tingling of the extremities, pruritus, vertigo or dizziness may occur. Reduction of dosage may alleviate symptoms. Therapy need not be discontinued, but such patients should be observed with extra care.

Warning: Patients should be cautioned not to drive vehicles or use hazardous machinery while on therapy.

Precautions: In cases of impaired or suspected renal impairment, use with greater caution and reduce dosage in proportion to extent of impairment. Transient elevations of BUN have been reported. As a routine precaution, appropriate blood studies should, therefore, be made during prolonged therapy.

As with all polypeptides, the possibility of muscular weakness, including apnea, due to inadvertent overdosage or normal dosage in the presence of impaired renal function, should not be overlooked. In cases of apnea, medication should be promptly discontinued and assisted respiration given until serum levels fall and normal breathing is restored.

Other antibiotics, such as kanamycin, streptomycin, dihydrostreptomycin, polymyxin, and neomycin, may also have varying neurotoxic or nephrotoxic potential. They should be used with great caution concomitantly with Coly-Mycin Injectable (colistimethate sodium).

For deep intramuscular injection only.

Dosage: By the I.M. route only, in 2 to 4 divided doses ranging from 1.5 to 5 mg./Kg./day (0.7 mg. to 2.3 mg./lb./day). Average adult dose is 2.5 mg./Kg./day (1.1 mg./lb./day). In the presence of bacteremia, septicemia, or other serious infection, greater than average doses may be required; however, maximum daily doses should not exceed 5 mg./Kg. (2.3 mg./lb.) where renal function is normal.

Not recommended against Proteus.

Colistin is also available (as colistin sulfate) in: Coly-Mycin® Pediatric for Oral Suspension (not for systemic use), and Coly-Mycin® Otic with Neomycin and Hydrocortisone.

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WARNER-CHILCOTT Morris Plains, New Jersey WC

for your "my head keeps spinning" patient
Edward Sorel

How often have you heard these common complaints, symptomatic of vertigo? "...been getting dizzy spells lately." "First the room starts turning. Then I feel like I have to throw up." "Just getting into a car makes me feel nauseated!" In any case, vertigo, with or without nausea, is distressing enough to your patient. And it represents a therapeutic as well as a diagnostic challenge for you.

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protects most patients against nausea and vertigo up to 24 hours with a single dose

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BOOKS RECEIVED

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It All Started with Hippocrates. A Mercifully Brief History of Medicine. Richard Armour, with illustrations by Campbell Grant. Price, $3.95. Pp. 136. New York: McGraw-Hill, 1966.

Peripheral Arterial Disease. Volume IV in the Series, Major Problems in Clinical Surgery. Wiley F. Barker, M.D., and J. Englebert Dunphy, M.D., Consulting Editor. Price, $8.50. Pp. 229, illustrated. Philadelphia: Saunders, 1966.

Epilepsy and the Law. A Report on Legal Reform in the Light of Medical Progress, revised 2nd ed. Roscoe L. Barrow and Howard D. Fabing, M.D. Price (paper), $5.95. Pp. 174. New York: Harper & Row (Hoeber Med. Div.), 1966.

Atlas of Hernia Repair. Carl H. Calman, M.D., F.A.C.S. Illustrated by Katherine Masterson. Price, $16.75. Pp. 159, illustrated. St. Louis: Mosby, 1966.

Questions and Answers in Orthopaedics. For Students, Interns, Residents, and Board Aspirants. Floyd G. Goodman, B.S., M.D., and George R. Schoedinger III, B.S., M.D. Price, $9.85. Pp. 244. St. Louis: Mosby, 1966.

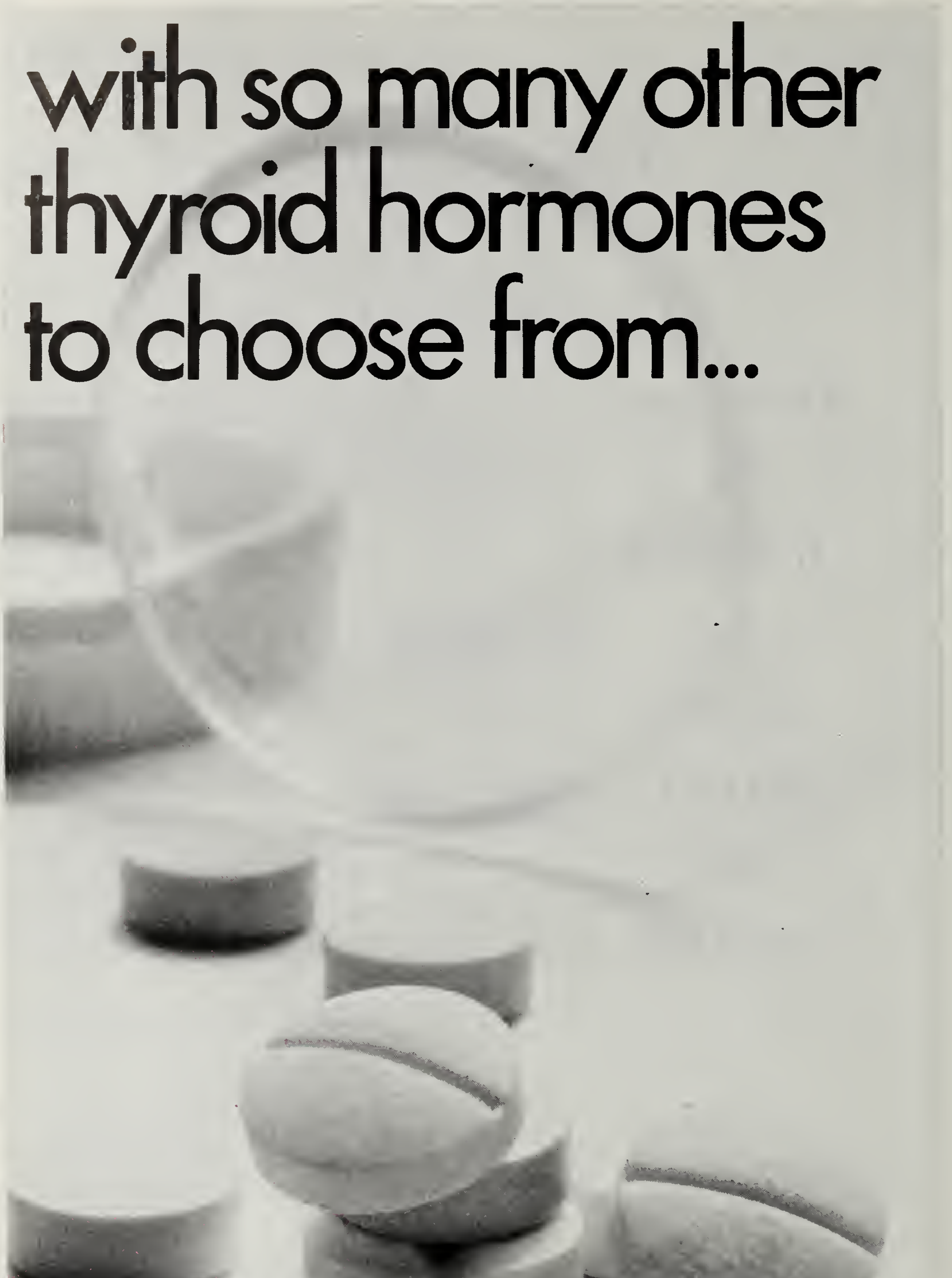
Ocular Pharmacology. William H. Havener, B.A., M.D., M.S. (Ophth.). Price, $21.75. Pp. 456, with 198 illustrations. St. Louis: Mosby, 1966.

The Ocular Fundus in Neurologic Disease. A Diagnostic Manual and Stereo Atlas. William Fletcher Hoyt, M.D., and Diane Beeston, A.B. Price, $35.00. Pp. 128, with 137 photographic illustrations, 98 stereoscopic views in full color on 14 View-Master® reels, and a View-Master® compact viewer. St. Louis: Mosby, 1966.

Early Management of Acute Trauma. Edited by Alan M. Nahum, M.D. Price, $21.00. Pp. 336, with 271 figures. St. Louis: Mosby, 1966.

Hematologic Problems in the Newborn. Volume IV in the Series, Major Problems in Clinical Pediatrics. Frank A. Oski, M.D., and J. Lawrence Naiman, M.D.; Alexander J. Schaffer, Consulting Editor. Price, $11.00. Pp. 294, with 47 illustrations. Philadelphia: Saunders, 1966.

Biological Treatment of Mental Illness. Proceedings of the II International Conference of the Manfred Sakel Foundation, held October 31 to November 3, 1962, at the New York Academy of Medicine, New York. Edited by Max Rinkel, M.D. Price, $25.00. Pp. 1025, illustrated. New York: Page (Farrar, Straus and Giroux), 1966.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The “Socio-geographic” mystery

Why is one man's gastric ulcer another man's duodenal?

Geographic variation in the *incidence* of peptic ulcer is a familiar fact. But the proclivity of certain *kinds* of ulcer for certain geographic areas is a recently recognized phenomenon.[1,2]

For example, in one particular Norwegian fishing village there is a tendency for patients to develop a gastric ulcer; anywhere else in Norway, ulcers are usually duodenal. Peruvians high in the Andes have more gastric ulcers than their compatriots in the lowlands. Why? Nobody knows.

Social variations, too. Even in the same geographic areas there are interesting variations. An Englishman's ulcer depends on his social standing—professional men suffer with duodenal ulcers, while workingmen have more of the gastric variety. In southern India the pattern is eversed. Here, duodenal ulcers are common among laborers and agricultural workers and rare among the upper classes.

Investigators are exploring every possible theoretical avenue in their search for the cause of peptic ulcer. Of all the factors implicated in ulcerogenesis, the one that is generally acknowledged to be of primary importance is hypersecretion of gastric acid.[3-8] Or, as one author states it: "The medical management of peptic ulcer pharmacologically is, in the final analysis, concerned largely with the effective inhibition of peptic activity."[3]

Robinul (glycopyrrolate) provides potent, rapid, specific antisecretory action confirmed by gastric analyses and x-ray evidence of clinical effectiveness.[3,7,9–12] Relieves pain with "impressive" promptness.[8] Quickly alleviates acute discomfort, nd effectively counteracts gnawing pain, preprandial midepigastric pain, elching and other ulcer symptoms.[7] Suppression of nocturnal pain is "outtanding."[13] Maximally effective doses may be given with minimal side eactions, and the incidence of unwanted anticholinergic effects is negligible.[3,7-14]

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Precautions: Administer with caution in the presence of incipient glaucoma.
Adverse Reactions: Dryness of the mouth, blurred vision, urinary difficulties, and constipation are rarely troublesome and may generally be controlled by reduction of dosage. Other side effects associated with the use of anticholinergic drugs include tachycardia, palpitation, dilatation of the pupil, increased ocular tension, weakness, nausea, vomiting, headache, dizziness, drowsiness, and rash.
Dosage: Dosage should be adjusted according to individual patient response. Average and maximum recommended dose is 1 tablet 3 times a day: in the a.m., early p.m., and at bedtime. *See product literature for full prescribing information.*
Supply: Robinul (glycopyrrolate 1 mg.); Robinul Forte (glycopyrrolate 2 mg.); Robinul-PH (glycopyrrolate 1 mg.) with phenobarbital 16.2 mg. (Warning: May be habit-forming); Robinul-PH Forte (glycopyrrolate 2 mg.) with phenobarbital 16.2 mg. (Warning: May be habit-forming.) In bottles of 100 and 500 scored tablets.
References: **1.** Jones, F. A., and Gummer, J. W. P.: Clinical gastroenterology, Springfield, Ill., Charles C Thomas, 1960, pp. 322-3. **2.** Bockus, H. L.: Gastroenterology, 2nd ed., vol. 1, Philadelphia, Saunders, 1963, p. 468. **3.** Sun, D. C. H.: Ann NY Acad Sci 99:153 (Feb. 28) 1962. **4.** Moore, V. A.: Postgrad Med 38:216 (Sept.) 1965. **5.** Dragstedt, L. R., Woodward, E. R., Storer, E. H., Oberhelman, H. A., Jr., and Smith, C. A.: Ann Surg 132:626 (Oct.) 1950. **6.** Posey, E. L., Jr., Smith, P., Turner, C., and Aldridge, J.: Amer J Dig Dis 10:399 (May) 1965. **7.** Lamphier, T. A., Siegel, L., and Goldberg, R. I.: Amer J Gastroent 37:551 (May) 1962. **8.** Kasich, A. M., and Fein, H. D.: Ibid 39:61 (Jan.) 1963. **9.** Epstein, J. H.: Ibid 37:295 (Mar.) 1962. **10.** Moeller, H. C.: Ann NY Acad Sci 99:158 (Feb. 28) 1962. **11.** Slanger, A.: J New Drugs 2:215 (Jul.-Aug.) 1962. **12.** Barman, M. L., and Larson, R. K.: Amer J Med Sci 246:325 (Sept.) 1963. **13.** Shutkin, M. W.: Amer J Gastroent 38:682 (Dec.) 1962. **14.** Fleshler, B.: J New Drugs 2:211 (Jul.-Aug.) 1962.

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NATIONAL AND REGIONAL MEETINGS

November 27–30: Clinical Convention of the American Medical Association. Las Vegas, Nevada. Address: Dr. F. J. L. Blasingame, *Executive Vice President*, 535 North Dearborn Street, Chicago, Ill. 60610.

November 27–December 2: Radiological Society of North America. Palmer House, Chicago. Address: Dr. Maurice D. Frazer, *Secretary*, 5145 O Street, Lincoln, Neb. 68510.

December 2–3: American Rheumatism Association, Interim Session. Netherland Hilton Hotel, Cincinnati. Address: Margaret M. Walsh, *Executive Secretary*, 1212 Avenue of the Americas, New York, N. Y. 10036.

December 3–8: American Academy of Dermatology. Americana Hotel, Bal Harbour, Fla. Address: Dr. Stanley E. Huff, *Secretary-Treasurer*, 636 Church Street, Evanston, Ill. 60201.

December 6–8: Southern Surgical Association. Boca Raton Hotel and Club, Boca Raton, Fla. Address: Dr. George H. Yeager, *Executive Secretary*, 314 Medical Arts Building, Baltimore, Md. 21201.

December 26–31: American Association for the Advancement of Science. Sheraton-Park Hotel, Washington, Address: Mr. R. L. Taylor, 1515 Massachusetts Avenue, N.W., Washington, D. C. 20005.

January 22–23: National Congress on the Socio-Economics of Health Care. Palmer House, Chicago. Address: Division of Socio-Economic Activities, American Medical Association, 535 North Dearborn Street, Chicago, Ill. 60610.

February 9–15: Congress on Medical Education. Palmer House, Chicago. Address: Dr. Walter S. Wiggins, American Medical Association, 535 North Dearborn Street, Chicago, Ill. 60610.

February 15–19: American College of Cardiology. Washington Hilton Hotel, Washington. Address: Mr. William D. Nelligan, Executive Director, 9650 Rockville Pike, Washington, D. C. 20014.

March 5–9: International Anesthesia Research Society (41st Congress). Americana Hotel, Bal Harbour, Fla. Address: Dr. B. B. Sankey, Executive Secretary, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

March 10–12: American Association of Pathologists and Bacteriologists. Sheraton-Park Hotel, Washington. Address: Dr. J. Lowell Orbison, University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. 14620.

March 12–15: International Academy of Pathology. Sheraton Park Hotel, Washington. Address: Dr. F. K. Mostofi, Secretary-Treasurer, Armed Forces Institute of Pathology, Washington, D. C. 20305.

March 12–15: 35th Annual Postgraduate Clinic of the District of Columbia Dental Society. Shoreham Hotel, Washington. Address: Ashur G. Chavoor, D.D.S., General Chairman, D. C. Dental Society, 1835 Eye Street, N.W., Washington, D. C. 20006.

fall 1966

DORSEY Season

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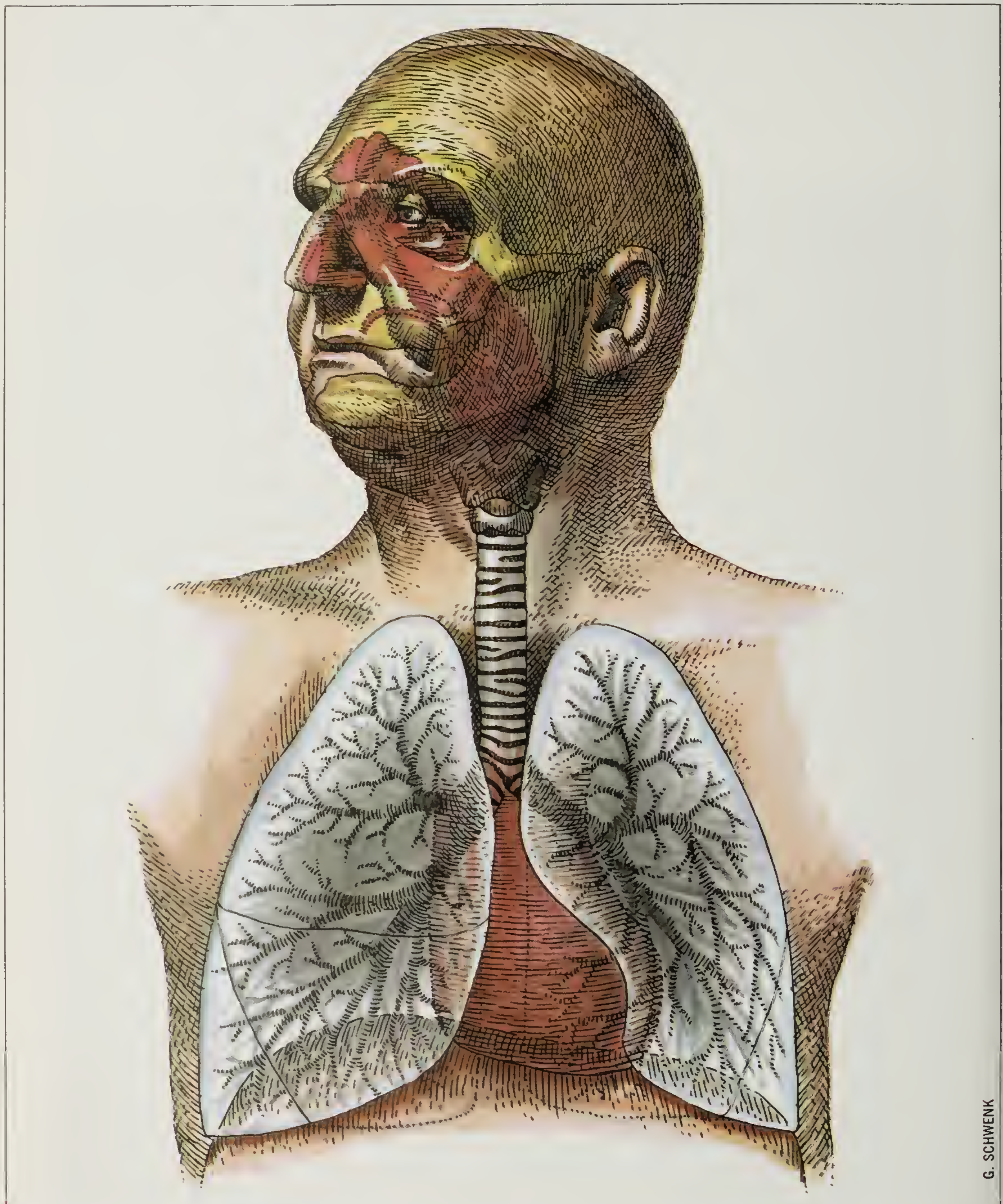
this issue: the common cold and the aging patient

the common cold and the aging patient

Louis J. Vorhaus, II, M.D., F.A.C.P.



Effects of aging on the anatomic and physiologic aspects of the respiratory apparatus.

The chest becomes more fixed, less mobile and less elastic as the bronchial walls and thoracic ligaments lose elasticity. The diaphragm and intercostal muscles atrophy and weaken. The lungs become smaller, flabbier and weigh less, decreasing vital and total lung capacity, increasing residual volume and the alveolar dead space.

Sir William Osler described pneumonia as the welcome friend of the aged patient, because the patient with pneumonia usually died quietly. But today, the well-informed physician is an even better friend of the aging patient, since it is better to live than to die, no matter how quietly.

One of the first avenues of approach in the control of the hazards of respiratory disease in the aging patient is prompt and proper attention to the common cold or upper respiratory infection. The common cold may be the first step in the relatively short path to lower respiratory infection, broncho-pneumonia and death. This train of events occurs frequently among older persons. Indeed, pneumonia is one of the most common causes of their admission to hospitals and ranks high on the list of geriatric killers. Colds are more debilitating in elderly people and the aged are more likely candidates for secondary infections such as sinusitis and bronchitis. These infections, in turn, are more prone to lead to broncho-pneumonia, because of lowered resistance and anatomic and physiologic changes in the lungs of the elderly.

What is different about the respiratory tree of an aged person and that of an otherwise healthy younger adult? Aging certainly takes its toll on all parts of the body, affecting both anatomic and physiologic aspects of the respiratory apparatus. These changes are in part due to the wear and tear that occurs over the years; the repeated bouts of respiratory infection, long exposure to atmospheric pollutants, to occupational inhalants, smoking, malnutrition, obesity, inactivity and the development of other diseases which may affect the lungs.

With the passage of years, the lungs change. They become scarred and emphysematous and lose their compliance. The whole chest becomes more fixed, less mobile and less elastic.

The anatomic changes that occur in aging render the lungs less efficient. Tests of pulmonary function in senescence show a deterioration characterized by a decrease in vital capacity and total lung capacity, an increase in residual volume and alveolar dead space. Maximum breathing capacity is reduced and uniformity of ventilation deteriorates. These problems are often aggravated by the obstructed breathing, fever and secondary infection associated with the common cold, placing an additional stress on the entire cardiopulmonary reserve.

In addition, the efficiency of a cough is below par in older persons even though they are in good health. This is partly due to the decreased respiratory excursions and distensibility of the chest wall, and partly from loss of elasticity of bronchial walls which tend to make them collapse in a cough.

The elderly patient's resistance to infection is often reduced. Nutritional deficiencies are more common in aged people. There is some evidence to indicate that their capacity to respond to stress is less efficient. Finally, there is often relatively meager symptomatic response to acute disease. The absence of obvious or dramatic clinical signs and symptoms of severe illness is particularly dangerous because, coming as it

(concluded on following page)

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does in a person whose defenses are weakened both locally and systemically, pulmonary disease may progress rapidly to irreversible stages before medical attention is sought. Respiratory infection is especially hazardous because the aged patient responds badly to hypoxia. Not only is his response to oxygen lack impaired, but the work of breathing, due to decreased compliance of the lung and increased stiffness of the thorax, is markedly augmented.

Many patients late in life are in a precarious and delicate cardiopulmonary balance which is easily decompensated from relatively minor insults such as colds and upper respiratory infections.

For all of these reasons, geriatricians long have stressed the importance of preventing respiratory insults. Today we have better ways of treating respiratory infection, improved techniques for clearing the lungs and bronchial tubes of secretions and better understanding of ways of improving ventilation. We possess a broader spectrum of antimicrobial agents including newer ones to deal with previously resistant organisms. Even so, the death rate from pneumonia is high in older people, and it is preferable to avoid the disease than to treat it. To do so, attention must be paid to the general maintenance of good health and all that implies, as well as to the prevention, elimination and treatment of associated conditions that predispose to or cause pneumonia such as chronic upper or lower respiratory infection, respiratory allergy, chronic sinusitis and exposure to inspired irritants.

Colds and other minor respiratory infections, which favor the development of broncho-pneumonia, should be treated vigorously and promptly, particularly those patients whose aging process has been accompanied by the development of chronic pulmonary disease. Upper respiratory passages should be cleared with decongestants. Sinuses should be drained adequately. And, when indicated, appropriate antimicrobial therapy should be instituted before serious infection of the lower respiratory tree supervenes.

In decades past it was understandable that physicians welcomed pneumonia for the aged patients because it offered them a quiet and peaceful demise. Today we recognize that in many cases, peaceful as it may have been, such deaths were often avoidable. With the current knowledge and understanding of the problems that respiratory infections impose on aging people, vigilant medical attention can often restore them to a vigorous, rewarding and productive life so that the many opportunities that exist today for people to enjoy their golden years are realized and not stolen by untimely death.

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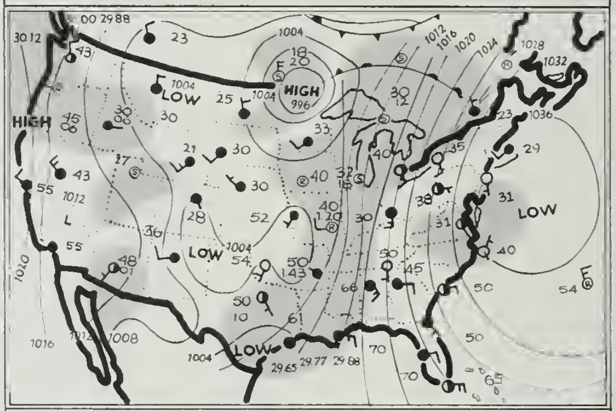
Weather Forecast Throughout the Nation



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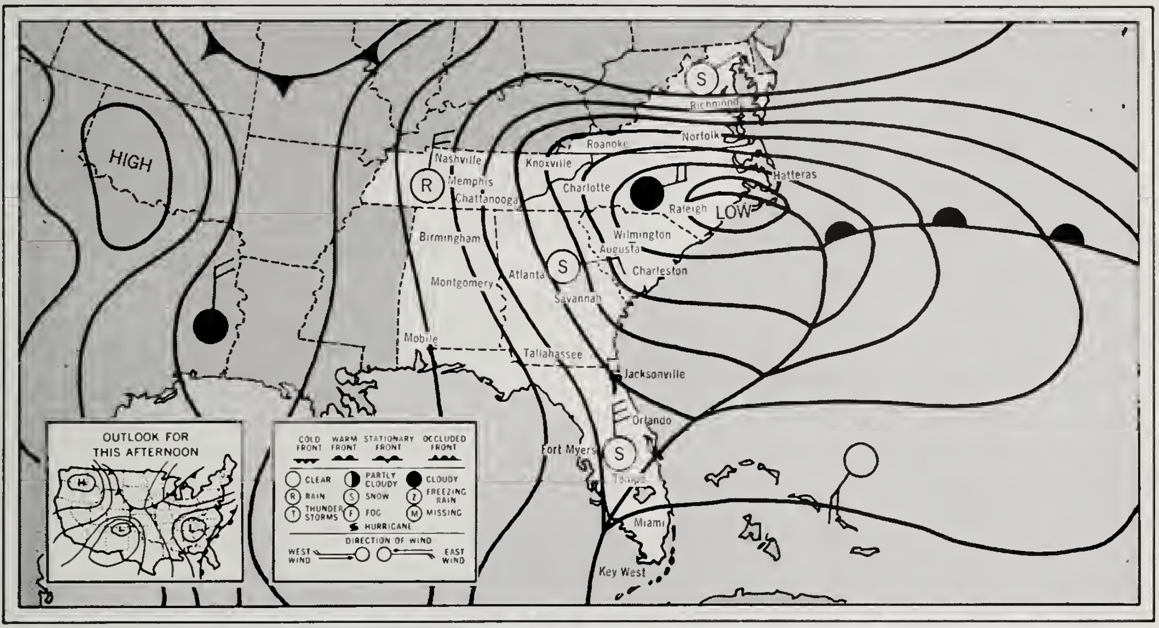
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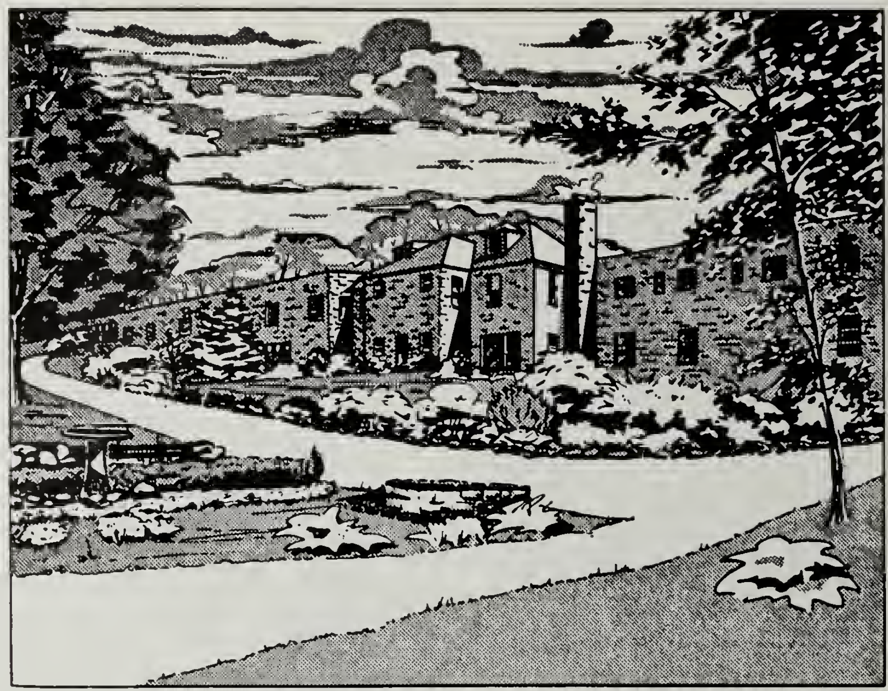

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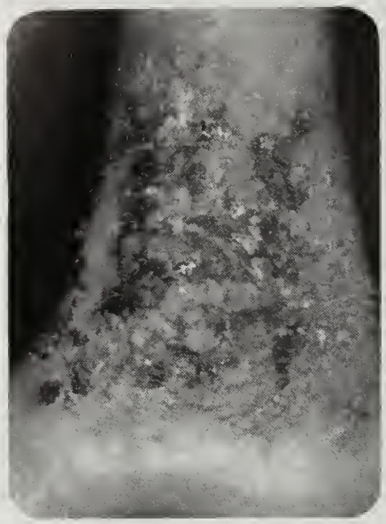
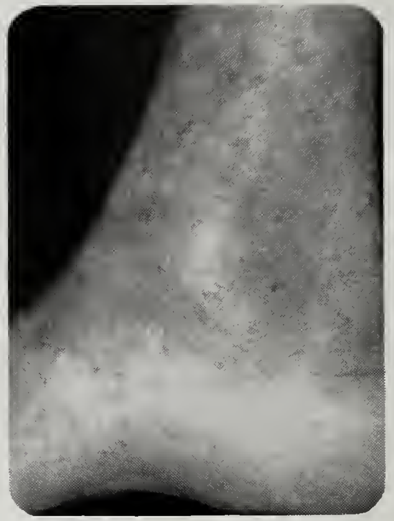
Warning: Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs. With administration of enteric-coated potassium supplements, the possibility of small bowel lesions should be kept in mind.
Precautions: Reduce dosage of concomitant antihypertensive agents by one-half. Discontinue if the BUN rises or liver dysfunction is aggravated. Electrolyte imbalance and potassium depletion may occur; take particular care in cirrhosis or severe ischemic heart disease, and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use with caution in patients with ulcerative colitis, gallstones, or bronchial asthma.
Side effects: Nausea, vomiting, diarrhea, muscle cramps, headaches and dizziness. Potential side effects include angina pectoris, anxiety, depression, drowsiness, hyperglycemia, hyperuricemia, lassitude, leukopenia, nasal stuffiness, nightmare, purpura, urticaria, and weakness.
For full details, see the complete prescribing information.
Availability: Bottles of 100 and 1000 tablets.

Geigy

eczema: scourge of childhood



R. R., Age 11—Before treatment—
atopic eczema of long standing



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Contraindications: Tuberculosis of the skin, herpes simplex, chicken pox and vaccinia.

Precautions and Side Effects: Do not use in the eyes or in the ear (if drum is perforated). A few individuals react unfavorably under certain conditions. If side effects are encountered, the drug should be discontinued and appropriate measures taken. Use on infected areas should be attended with caution and observation, bearing in mind the potential spreading of infection and the advisability of discontinuing therapy and/or initiating antibacterial measures. Generalized dermatological conditions may require systemic corticosteroid therapy. Steroid therapy, although responsible for remissions of dermatoses, especially of allergic origin cannot be expected to prevent recurrence. The use over extensive body areas, with or without occlusive nonpermeable dressings, may result in systemic absorption. Appropriate precautions should be taken. When occlusive nonpermeable dressings are used, miliaria, folliculitis and pyodermas will sometimes develop. Localized atrophy and striae have been reported with the use of steroids by the occlusive technique. When occlusive nonpermeable dressings are used, the physician should be aware of the hazards of suffocation and flammability. The safety of use on pregnant patients has not been firmly established. Thus, do not use in large amounts or for long periods of time on pregnant patients.

Packages: Tubes of 5 Gm. and 15 Gm.; ½ lb. jar.

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Reference: 1. Roberts, C. E., Jr.; Perry, D. M.; Kuharic, H. A., and Kirby, W. M. M.: A. M. A. Arch. Int. Med. 107:204 (Feb.) 1961.

*bidCAPS is a trademark of Bristol Laboratories, Division of Bristol-Myers Company, for its brands of twice-a-day capsules. Each Tetrex bidCAP contains Tetrex (tetracycline phosphate complex) equivalent to 500 mg. tetracycline HCl activity.

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Four hundred and fifty patients, most of them classified as functional neurotics, were treated with hydroxyzine for periods of five months to four and one-half years. Sustained good-to-excellent relief from symptoms of anxiety and tension was attained in 401 (89%) of the series. *"Cumulative effects, habituation or addiction to hydroxyzine was not noted during the entire period of this study."*

Shalowitz, M.: Int. Rec. Med. 174:357, June, 1961.

Even in the classically dependent alcoholic...

Vistaril (hydroxyzine) was evaluated for relief of postalcoholic syndrome in 52 chronic alcoholic outpatients over a period of two to four weeks. Many patients received partial to complete relief of psychomotor agitation, anxiety, irritability, craving, insomnia, depression, anorexia, nausea and tension. "*No evidence of toxicity or habituation was noted.*" "*No difficulty was experienced in discontinuing medication.*"

Greenhouse, H. R.: Med. Times 91:1069, November, 1963.

Of 326 alcoholics treated with hydroxyzine for the postalcoholic syndrome, satisfactory control was achieved in 276 (85%). "*As is not the case with other tranquilizers, hydroxyzine has no published record of causing addiction and dependence or withdrawal symptoms.*" Goldman, H. I.: Southwest. Med. 42:276, June, 1961.

Even in the institutionalized patient needing long-term treatment...

ne hundred and fifty-two institutionalized emale patients were studied on long-term, igh-dose therapy.

ven at high dosages, hydroxyzine *. . . did not produce either euphoria or depression."*

apolla, A.: Clin. Med. 8:1332, July, 1961.

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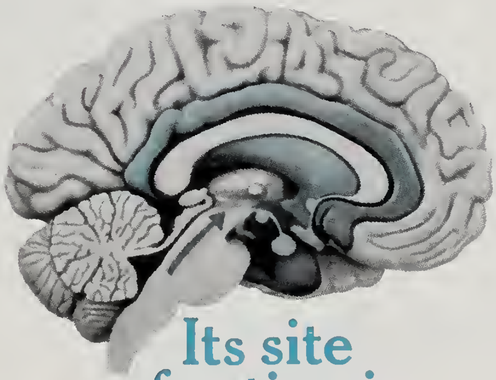

Its site of action is the seat of anxiety

turn page for brief summary...

BRIEF SUMMARY

Contraindications: Hypersensitivity to hydroxyzine. The parenteral solution, for intramuscular or intravenous use, *must not* be injected subcutaneously or intra-arterially.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available, to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants. In conjunctive use, dosage for these drugs should be decreased, as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. On reported intravenous injection a few instances of digital gangrene have occurred distal to the injection site, considered to be due to inadvertent intra-arterial injection or possibly periarterial extravasation. Therefore, particular caution should be observed to insure injection only into intact veins; avoid either intra-arterial injection or extravasation. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity has been reported in some hospitalized patients given higher than recommended dosage.

When this product is given intravenously undiluted, minimal amounts of intravascular hemolysis occur at the site of injection. Giving the maximum recommended intravenous dose (100 mg.) to adults results in immediate transient hemolysis with the liberation of a total of 2-3 grams of hemoglobin, which, in some individuals, can cause small amounts of hemoglobinuria. This compares with the normal red cell destruction from which approximately 8 Gm. of hemoglobin are liberated every 24 hours. If the hydroxyzine is diluted with 50 cc. of normal saline and given during a period of four minutes or more, this phenomenon does not occur.

Supply: Vistaril (hydroxyzine pamoate) Capsules: Equivalent to 25 mg., 50 mg., 100 mg. hydroxyzine HCl. Vistaril (hydroxyzine pamoate) Oral Suspension: Equivalent to 25 mg. hydroxyzine HCl per 5 cc. teaspoonful. Vistaril (hydroxyzine HCl) Parenteral Solution: 25 mg./cc.—10 cc. vial and 50 mg./cc.—2 cc. and 10 cc. vial; Isoject,® 25 and 50 mg. per cc., 1 cc. per unit.

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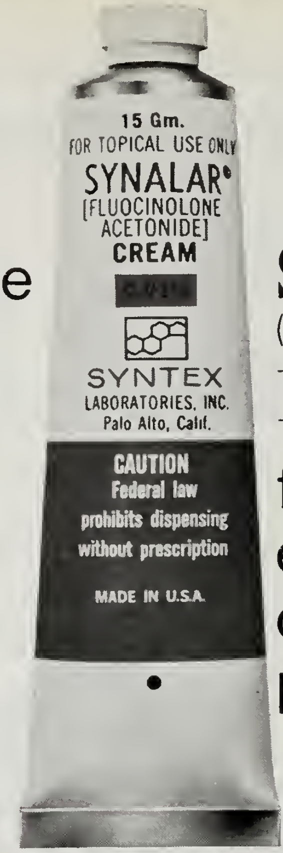

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Now you can prescribe as little or as much Synalar Cream 0.01% as is needed for a particular therapeutic problem in a size that permits the greatest economy for your patient. The new 15 Gm. tube, for example, is best suited for short-term therapy and for small sites. For more extensive body areas prescribe the 45 Gm. tube—a size that's also ideal for your treatment table. And the 120 Gm. jar is most economical for hospital use. Thus, with Synalar Cream 0.01%, you have the superiority of a modern topical corticosteroid shown to be more effective than 1% hydrocortisone[1-3] plus the economy that makes therapy practical for use in more dermatologic conditions, in long-term maintenance, with occlusive dressings in resistant cases, and in extensive area involvement.

Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of its components. **Precautions:** 1. *General*—Synalar Cream 0.01% is virtually nonsensitizing and nonirritating. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to
have an adverse effect on pregnancy, the safety of their use on pregna
females has not absolutely been established. Therefore, they should not b
used extensively on pregnant patients, in large amounts, or for prolonge
periods of time. 2. *Occlusive dressing method*—With occlusion of extensiv
areas, systemic absorption of the corticosteroid may occur, and suitab
precautions should be taken. Occasional patients may show contact sen
tivity to a particular dressing material or adhesive. Miliaria, folliculitis,
pyodermas have been seen infrequently with the use of this technique. Th
development of infection requires appropriate antibacterial therapy and d
continuation of the occlusive dressing method. Local atrophy and stria
have been reported with protracted occlusive dressing therapy. While lesic
relapses can be expected to occur in many psoriatic patients, remissior
may persist for several weeks to several months in favorable cases. Th
patient whose psoriasis is in an active stage, with recent appearance of ne
lesions, may not be a good candidate and may show early relapse. Som
plastic films may be flammable, and due care should be exercised in the
use. Similarly, caution should be employed when such films are used on
left near children to avoid the possibility of accidental suffocation. **Sic
Effects:** Side effects are not ordinarily encountered with topically applie
corticosteroids. As with all drugs, however, a few patients may react un
vorably to Synalar under certain conditions. **References:** 1. Cahn, M. M., ar
Levy, E. J.: J New Drugs 1:262 (Nov.-Dec.) 1961. 2. Meenan, F. O.: J Iris
Med Ass 52:75 (Mar.) 1963. 3. Robinson, H. M., Jr., Raskin, J., and Dunsea
W. J. R.: Southern Med J 56:797 (Jul.) 1963.

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SQUIBB NOTES ON THERAPY

"'Tranquilizer' is not a good word"[1]

"THIS classification is psychologically too seductive, pharmacologically too unspecific, and in terms of results not infrequently untrue."[2]

What is a tranquilizer? According to the 24th Edition of Dorland's Medical Dictionary[3] a tranquilizer is "an agent which acts on the emotional state, quieting or calming the patient without affecting clarity of consciousness."

Defining a drug by its effects, however, can be misleading. The same effects by which the dictionary defines a tranquilizer have sometimes been seen after administration of a sedative — or, for that matter, a placebo.

Ambiguous though the term may be, it appears to be here to stay. The 1966 edition of the Physicians' Desk Reference[4] lists 42 tranquilizers indicated for treatment of anxiety and apprehensive states.

'Tranquilizers' have differences in action, differences in effect

Although all tranquilizers are intended to calm anxious patients there *are* differences in their actions — and in their effects. They have been divided into three categories — the rauwolfia group, the 'minor' tranquilizers, and the phenothiazines.[5]

Although the tranquilizing effect of rauwolfia has been known for centuries, its use as an antipsychotic agent in current practice has diminished.[5]

A 'minor' tranquilizer is often prescribed to achieve more than one effect. Thus, besides being tranquilizers some of these compounds may be muscle relaxants, antihistaminics with some calming action, anticholinergic sedatives, or antispasmodics.[5]

The phenothiazines are considered 'major' tranquilizers because they alter psychotic behavior.[1] This classification may have done them more harm than good because it implies that the phenothiazines should be reserved for the more severely disturbed. This is not necessarily true.

The phenothiazines — and the problem of sedation

One of the problems of prescribing phenothiazines for ambulatory patients has been the fear that excessive sedation will impair the patient's ability to function. This, however, is less of a problem with some of the phenothiazines.

"Clinically they may be differentiated primarily in terms of their potency and the extent of their sedative effect, which appear to be inversely proportional. That is, the least potent, the one which is used in highest dosage, chlorpromazine, is the most sedative, while the reverse holds true for fluphenazine."[6]

In a recent report on various studies conducted over several years evaluating 360 patients treated for anxiety and stress with seven phenothiazines, this inverse relationship of potency to sedation was confirmed.[7] Also under consideration was the degree to which the particular phenothiazines neutralized anxiety (the angolytic index). Interestingly enough there was, again, an inverse relationship. The most sedative of the phenothiazines appeared to be the least active in neutralizing anxiety. Fluphenazine, one of the least sedative, on the other hand, was found to be most effective in relieving anxiety.[7]

RELATIVE SEDATIVE AND ANGOLYTIC INDICES OF PRINCIPAL PHENOTHIAZINES*

DRUG	SEDATIVE INDEX	ANGOLYTIC INDEX	BASED ON STANDARD DOSE OF
Chlorpromazine	100	15	25 mgs.
Triflupromazine	100	15	25 mgs.
Thioridazine	90	17	25 mgs.
Perphenazine	15	25	4 mgs.
Carphenazine	25	25	25 mgs.
Trifluoperazine	3.3	95	2.0 mgs.
Fluphenazine	3.5	100	2.5 mgs.

*adapted from Sainz[7]

Prolixin is therapeutically effective without excessive sedation

When used as a 'tranquilizer' in general medical practice, in many patients Prolixin (Squibb Fluphenazine Hydrochloride) suppresses anxiety, but not normal activity. These two features are of particular importance to patients who must be able to live and work without their normal daily activities being restricted.

Because of its longer duration of action, Prolixin, in doses of as little as one to three milligrams in adults, generally taken once a day, is effective in maintaining many patients free of their symptoms of anxiety and tension.

Contraindications: Do not use with high doses of hypnotics or in patients with subcortical brain damage. Use with caution in patients with a history of convulsive disorders. Severe reactions may occur in patients with idiosyncrasy to other centrally-acting drugs, and severe hypotension may occur in patients with special medical disorders, e.g. mitral insufficiency and pheochromocytoma.

Precautions: Effects of atropine, anesthetics and C.N.S. depressants may be potentiated. Hypotension may occur in patients undergoing surgery. Do not use epinephrine for treatment of the hypotensive reactions which may appear in patients on phenothiazine therapy.

Side Effects: Extrapyramidal reactions, allergic skin reactions, the possibility of anaphylaxis, drowsiness, visual blurring, dizziness, insomnia, nausea, anorexia, salivation, edema, perspiration, dry mouth, abnormal lactation, polyuria, hypotension, and jaundice and biliary stasis may occur. Routine blood counts are recommended to determine possible blood dyscrasias; if symptoms of upper respiratory infection occur, discontinue drug and institute appropriate therapy.

Available: 1 mg. tablets. Bottles of 50 and 500.

For full prescribing information, see package insert

References: 1. Simpson, G.M.: Postgrad. Med. *39*:557, 1966. 2. Freyhan, F.A.: Am. J. Psychiat. *115*:577, 1959. 3. Dorland's Illustrated Medical Dictionary, ed. 24, Philadelphia, W. B. Saunders Co., 1965, p. 1603. 4. Physicians' Desk Reference, 1966, Oradell, N.J., 1965, p. 310. 5. Cohen, S.: Northwest Med.. 65:197, 1966. 6. Detre, T., and Jarecki, H.: Connecticut Med. 25:553, 1961. 7. Sainz, A.: Psychosomatics 5:167, 1964.

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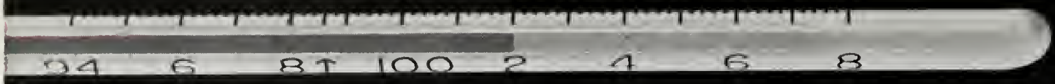

two to four times
the therapeutic
activity of other
erythromycins

CONTRAINDICATIONS: Ilosone is contraindicated in patients with a known history of sensitivity to this drug and in those with preexisting liver disease or dysfunction.

SIDE-EFFECTS: Even though Ilosone is the most active oral form of erythromycin, the incidence of side-effects is low. Infrequent cases of drug idiosyncrasy, manifested by a form of intrahepatic cholestatic jaundice, have been reported. There have been no known fatal or definite residual effects. Gastro-intestinal disturbances not associated with hepatic effects are observed in a small proportion of patients as a result of a local stimulating action of Ilosone on the alimentary tract. Although allergic manifestations are uncommon with the use of erythromycin, there have been occasional reports of urticaria, skin eruptions, and, on rare occasions, anaphylaxis.

DOSAGE: *Children under 25 pounds*—5 mg. per pound of body weight every six hours. *Children 25 to 50 pounds*—125 mg. every six hours. *Adults and children over 50 pounds*—250 mg. every six hours. For severe infections, these dosages may be doubled.

Available in Pulvules®, suspension, drops, and chewable tablets. Ilosone Chewable tablets should be chewed or crushed and swallowed with water.

Additional information available to physicians upon request.
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MEDICAL ANNALS
of the District of Columbia

November 1966 VOLUME XXXV • NUMBER 11

The Functioning Carcinoid Tumor: A Serendipity in Diagnosis*

THOMAS W. MATTINGLY, M.D., F.A.C.P.†, E. COWLES ANDRUS, M.D., F.A.C.P.‡,
AND (BY INVITATION) GUNNAR BIÖRCK, M.D.§, AND WILLIAM C. MANION, M.D.||

IN THE COINAGE of the term "serendipity" Walpole in a letter to Mann in 1754 stated that he formed it from the title of a fairy story, "The Three Princes of Serendip," because the Princes "were always making discoveries, by accident and sagacity, of things they were not in quest of."[1] Before our readers get the idea that we consider ourselves as sagacious princes, we should like to make it clear that we are using this term in a more popular definition—"to denote the faculty of making lucky and unexpected finds by accident." Had we been wise princes we would have solved the problem much sooner. In this instance we set out to make a diagnosis of a cardiac disease which could be the cause of long-standing liver and gastrointestinal disease (ascites) when by accident we found a type of intestinal and liver disease which caused the heart disease. Although the term serendipity is most often used in relation to research, it applies more frequently in clinical medicine.

The subject of our narration and diagnostic adventure was a white woman who was 32 years of age when first admitted to Johns Hopkins Hospital on the service of one of us (E.C.A.) in 1949. Symptoms began at the age of 10, but it has been impossible to obtain documentary medical records prior to 1949 and the early symptoms are derived chiefly from the history given by the patient.

At the time of her hospital admission in 1949 the following problems engaged the attention of the staff:

1. Clinical features of valvular heart disease and congestive failure.
2. Persistent hepatomegaly and ascites after maximum response to therapy for congestive failure.
3. Scar of old rib resection for drainage of empyema and/or subphrenic abscess, residual pleural thickening and poorly functioning diaphragm, all in the right hemithorax and diaphragmatic areas, considered to be residuals of thoracic disease at the age of 17 years.
4. Peculiar vasculocutaneous lesions which by history began about the age of 12 years.
5. Pronounced emotional instability and anxiety state.

Pertinent cardiac history at that time indicated the presence of "growing pains" in childhood, history of the onset of the vasomotor phenomena manifested by periodic flushing of the face which began at the age of 12, first observation of a heart murmur during a pregnancy in her twenties which was considered a functional murmur; later, after the development of a permanent bluish discoloration of the skin about the cheeks, a congenital heart lesion was considered. Features of congestive failure developed 2 years prior to admission, and the ascites was noted 1 year prior to admission. A right heart catheterization was performed in the laboratory of Dr. Richard Bing. His findings and conclusions were as follows:

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1. No evidence of a left-to-right shunt.

2. Ninety-one per cent arterial O_2 saturation, indicating small right-to-left shunt.

3. Moderate right ventricular hypertension of 64/10 mm. Hg with only slight elevation of right ventricular diastolic pressure, indicating little if any right ventricular failure.

4. Pulmonary artery pressure at the upper limits of normal with an unequivocal increase in systolic pressure as the catheter was pulled into the right ventricle on 2 occasions, indicating the presence of a mild pulmonary stenosis.

5. The normal to slightly elevated pulmonary artery pressure with low pulmonary artery flow indicating either an increase in pulmonary vascular resistance or in left atrial pressure.

6. Slightly low systemic flow and moderately low pulmonary flow with small right-to-left shunt.

7. Elevated right atrial pressure with high pulse pressure which may indicate tricuspid regurgitation.

8. Small rise in O_2 consumption per liter ventilation with exercise.

Conclusions: Pulmonic stenosis of relatively mild degree, sufficient to decrease the pulmonary blood flow but not sufficient to cause a fall in the oxygen consumption per liter of ventilation.

The clinical and hemodynamic features suggested congenital pulmonary stenosis, but the additional presence of a presystolic sound raised a question of a mitral valve lesion and therefore a rheumatic component as well.

The patient was discharged on a program of medical therapy for the congestive failure. An additional short period of hospitalization was made in 1950 for reëvaluation. The following diagnoses were made after these 2 hospitalizations:

1. Congenital heart disease, with pulmonic stenosis of the infundibular type.

2. Question of patency of foramen ovale or of small high ventricular septal defect.

3. Tricuspid regurgitation, secondary to right ventricular hypertension and question of mitral stenosis.

4. Acrocyanosis.

5. Peripheral vasomotor phenomenon.

6. Anxiety state.

7. Diverticulum of the duodenum.

Persistent edema, dyspnea, fatigue and ascites requiring paracentesis continued in spite of good medical therapy. She was readmitted to Johns Hopkins Hospital for reëvaluation with consideration for cardiac surgery in 1952, but the presence of persistent unexplained fever and an additional abnormality in the right side of the chest with a pleural effusion directed attention to these problems. Repeated venous and arterial blood cultures as well as cultures of fluid from the right pleural cavity failed to grow organisms. Other clinical features of bacterial endocarditis or a systemic infection failed to develop. Repeated leukocyte counts were between 4,000 and 8,000, but the sedimentation rates remained persistently elevated.

Repeated roentgenographic studies of the chest, abdomen, gastrointestinal tract and gallbladder failed to identify specific abnormalities except for a fixed elevation of the right hemidiaphragm, loculated fluid in the right pleural cavity, and progressive thickening of the pleura in the right hemithorax. The heart size remained at the upper limit of normal without evidence of calcification of the pericardium or features suggestive of external cardiac constriction by fluoroscopy and kymography. During one gastrointestinal study an examiner noted "2 small radiolucent areas in the region of the liver just to the right of the interspace between T-11 and 12" and it was his impression that they possibly represented abscesses in the liver. As will be noted later, this was probably correct.

There was no overt clinical response to repeated courses of antibiotics, the fever gradually lessened but was present when the patient was discharged on the thirty-eighth day of hospitalization. The cause of the fever and abnormality in the right side of the chest and subdiaphragmatic areas was not determined. She continued under observation and treatment at an Air Force Base Hospital since her husband was now on active duty. Periodic consultation and follow-up examination were made by one of us (E.C.A.).

Although only limited definitive studies were performed on the cardiovascular system during the last 1952 admission to Johns Hopkins Hospital because of the above complications, much thought was given to the exact nature of the heart disease, its relationship to the chronic chest disease, the hepatomegaly, the ascites, and the persistent peripheral edema. Some of the impressions and thinking of the staff have been gained from consultation notes and progress notes, a few of which are quoted.

The consultation note of Dr. Helen Taussig on March 20, 1952 read as follows:

"It is my impression that she has evidence of a mild degree of pulmonary stenosis with a minimal right-to-left shunt, without a greatly increased pressure in the right ventricle and without marked right ventricular hypertrophy. I thought that her ascites and edema must be due to pressure on the inferior vena cava, and it would seem logical to me to believe that it was associated with the old empyema and adhesions and diaphragmatic paralysis. Certainly the immediate problem today is to relieve the edema and ascites and pleural effusion, and thereafter to reëvaluate the situation. It is very much more the syndrome of a Pick's disease than of a valvular pulmonary stenosis. I hope very much that Dr. Blalock will be able to operate on the right chest and relieve the adhesions and relieve the ascites and edema. I honestly doubt that she needs to have her valvular pulmonary stenosis operated on, but I can better evaluate that after her ascites and pleural effusion have been relieved."

Dr. Victor A. McKusick made a note on April 1, 1952 as follows:

> "I don't feel confident that we have conclusively decided between congenital and rheumatic heart disease, assuming that it is one or the other. A sound of presystolic timing was recorded by Dr. Milnor in 1949. Pulmonary capillary pressure was never determined apparently. The present fever might conceivably be due to rheumatic recrudescence. The skin lesions suggest acne rosacea to me."

He suggested a number of pertinent studies and investigations, including an effort to obtain records from earlier admissions in hospitals in Baltimore and New Jersey—a recommendation which, if completed, might have given definite clues to diagnosis.

The following note is taken from a summary sent to the Air Force Base Surgeon by E.C.A. in June 1952:

> "We are all very much interested in Mrs. C's condition but are frankly perplexed as to the cause of the persistent enlargement of the liver and ascites. The degree of pulmonic stenosis does not seem to account for the amount or progress of the congestive failure."

Thus, when this patient was first admitted to the Cardiology Service of one of us (T.W.M.) at Walter Reed General Hospital in July 1952 through the efforts of E.C.A., we were confronted with these perplexing problems. The additional diagnostic cardiovascular studies planned by the Johns Hopkins Hospital staff were performed at Walter Reed General Hospital. They included another right-heart catheterization, a venous angiocardiogram, and a venogram of the inferior vena cava, the latter being performed in an effort to identify the cause of the greatly elevated venous pressure (now persistently around 300 mm. of water), the ascites and edema. The results of the right-heart catherization were essentially the same as those found at Johns Hopkins Hospital in 1949 except that the gradient across the pulmonary valve was less and the pressure in the right atrium higher. The character of the pressure studies indicated tricuspid insufficiency of a severe degree. The venous angiocardiogram of the right heart demonstrated the pulmonic stenosis to be valvular and not infundibular. The venogram of the inferior cava performed via the left femoral vein demonstrated a delayed entry of the contrast medium in the right atrium with excellent visualization of well-established collateral return into the vertebral system of veins, suggesting some interference with normal venous return. A specific point of constriction or blockage of the vena cava was not identified. We were likewise puzzled by the pronounced degree of the tricuspid insufficiency, high systemic venous pressure, pronounced hepatomegaly, ascites, peripheral edema, and peculiar cyanosis with so mild a degree of pulmonary valve stenosis. The initial diagnostic impression at Walter Reed General Hospital was that we were dealing with combined etiologies of congenital and acquired heart disease with a congenital pulmonary stenosis and acquired rheumatic heart disease of the tricuspid and less so of the mitral valves. The hepatomegaly and ascites were attributed to the severe tricuspid insufficiency.

On July 22, 1952 a conference was held between the staffs of the Johns Hopkins Hospital and Walter Reed General Hospital (Drs. Andrus, Mattingly, Blalock and Cooley participating), at which time the additional diagnostic information was reviewed. It was the consensus that the patient's total clinical picture could not be explained on the basis of the pulmonary stenosis alone and therefore surgical correction of this lesion would not provide any significant change in her condition and also that surgery would be hazardous with the present state of ventilation of the right lung. The final impression of the group was that there was a mild pulmonary stenosis present and possibly a mild right-to-left shunt and that a severe tricuspid insufficiency was the important lesion. The etiology of this lesion was not understood but was thought possibly to be on a rheumatic basis. It was agreed to continue on medical management for the failure.

Just after this, however, serendipity played a part in the next events which brought us nearer to a correct diagnosis. While E.C.A. was vacationing in the hills of New Hampshire in August 1952, one of us (T.W.M.) happened to read a short case report published in the July 1952 issue of the *American Heart Journal* in which Biörck, Axen and Thorson[2] reported a case of "Unusual cyanosis in a boy with congenital pulmonary stenosis and tricuspid insufficiency. Fatal outcome after angiocardiography." The autopsy findings revealed an ileal carcinoid with metastasis to the liver. The article included a short discussion as to possibilities of causal relationship or simple coincidence of the 2 conditions. An addendum mentioned other cases with metastatic carcinoids in the liver with the peculiar cyanosis but without heart valve lesions.

This short article was cut out of the journal, a short note appended and mailed to E.C.A., calling his attention to the similarity to our patient. He concurred in the possibility of a metastatic carcinoid in our patient. About this time the patient's recurring emotional upheavals and psychotic manifestations became so much of a problem (as they had been throughout most of her adult life) that an additional search for an intestinal carcinoid by surgical exploration was out of question. Our problem became that of medical management until we could obtain more stability in her mental and emotional state. A course of radioactive I^{131} was even considered at this point to aid in therapy of the congestive failure during this difficult period.

A second conference followed with Dr. Taussig when she returned from her vacation in October 1952. She became very much interested in the possibility of surgical correction of the tricuspid insufficiency and sought opinons on this subject. In this respect a very interesting correspondence took place between Dr. Taussig and Dr. Allan Friedlich of Massachusetts General Hospital in Boston, formerly of the staff at Johns Hopkins Hospital and who had been in Bing's laboratory at the time of the initial study. Dr. Taussig outlined the problem as existing at that time. Dr. Friedlich in his reply indicated that he had discussed the problem of tricuspid valve surgery with Drs. Dexter and Eppinger at the Peter Bent Brigham Hospital. They indicated that Dr. Dwight Harken had operated on a few cases of tricuspid stenosis but not regurgitation, but they both thought that Dr. Harken would not hesitate to undertake anything that was suggested. Dr. Friedlich in his armchair discussion of the findings as presented at that time correctly postulated "that a given degree of pulmonary stenosis might produce less right ventricular hypertension if tricuspid regurgitation was also present and that one might under these circumstances underestimate the degree of pulmonary stenosis."

This is as near as our patient came to Boston or of receiving a Boston opinion during all her years of medical illness and travels.

By July 1954 the additional reports of patients with proven metastatic functioning carcinoid tumors with cardiac involvement and flushing (carcinoid syndrome) by Thorson et al,[3] Waldenström and Ljungberg,[4] Isler and Hedinger,[5] the identification of 5-hydroxytryptamine (serotonin) as the specific hormone of the enterochromaffin-cell system of the small intestine by Erspamer and Asero[6] in 1952, and the isolation of serotonin from carcinoid tumors by Lembeck[7] in 1953 provided a sound basis for the clinical entity of functioning carcinoid tumor. These observations and publications strengthened our conviction that our patient had a functioning metastatic carcinoid tumor which could, in the light of recent knowledge, explain the entire clinical picture to include the hepatomegaly, ascites, cardiac lesions and myocardial failure, the peculiar flushing and telangiectasia of the skin of the face, and the emotional and psychiatric manifestations.

In September 1954 the Second World Congress of Cardiology was held in Washington, D. C., bringing to that city by chance some of the clinicians and investigators from Europe who had made these observations and publications. G.B. was attending, and he was included in a selected group of visiting physicians invited to a luncheon at Walter Reed General Hospital on September 15, 1954, following which a demonstration of teaching aids in auscultation was given by Dr. J. Scott Butterworth and T.W.M. Our patient was presented as a case of pulmonary stenosis, tricuspid insufficiency, and atypical cyanosis with metastatic carcinoid of the liver and probable carcinoid of the small intestine. She underwent her usual flushing episodes during the emotional stress of appearing before the large group of physicians (figure 1). Dr. Biörck concurred in our clinical diagnosis. Others in attendance remarked that they had seen a similar type of flushing but had not recognized the cause. Following this demonstration G.B. visited the Clinical Center at the National Institutes of Health during his stay in Washington, D. C., where he visited the laboratory of Drs. Udenfriend and Sjoerdsma who were doing research on

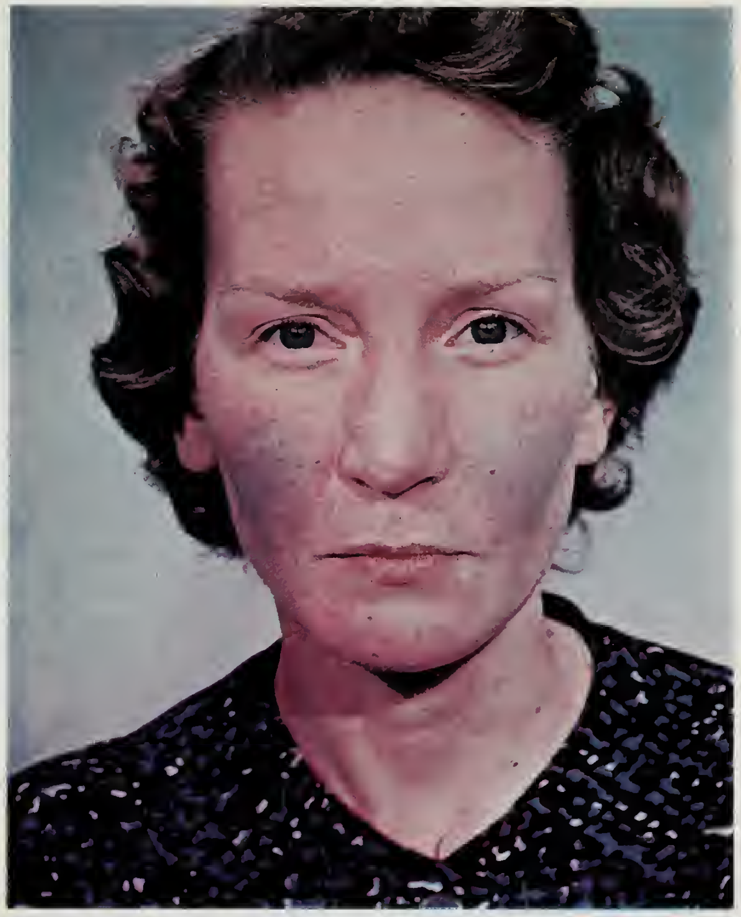

FIG. 1. Vasculocutaneous lesions as seen in 1954 (age 37) during an episode of flushing. Note the brick red to magenta color of the diffuse transient flush as superimposed on the chronic persistent bluish discoloration of the telangiectasia about the cheeks and forehead giving an initial impression of cyanosis but with no cyanosis of lips but conjunctival suffusion and active lacrimation. Periodic flushing began at age 12 years, the telangiectasia at about age 30.

serotonin. He informed these investigators that there was a patient with a functioning carcinoid tumor at Walter Reed General Hospital. Thus again, serendipity came into the picture.

G.B. came all the way from Sweden to inform our neighbors just 5 miles away that we had the very patient they were seeking for study. A few days later (September 21, 1954) a phone call came to the secretary of T.W.M. from Dr. Udenfriend stating that he understood that we had a patient with a carcinoid and that he might be able to help us in the diagnosis. A few days later he came to the office of T.W.M. with a few test tubes and reagents. Our patient brought in a specimen of her urine, and a urine specimen from T.W.M. was used as a control. Dr. Udenfriend performed his urinary test for 5 HIAA on these 2 specimens; the patient's gave a strongly positive test, the control gave a negative test. Thus the practicability of this test as a useful screening test for abnormal amounts of serotonin metabolites in the urine in a functioning carcinoid tumor was established. Our patient was subsequently admitted to the Clinical Center, National Institutes of Health in Bethesda, where detailed studies of serotonin metabolism were conducted. The results of these basic studies were later published by Sjoerdsma et al.[8] Our patient was case 1 in their case reports.

With these chemical and metabolic studies the previous clinical diagnosis of a functioning metastatic carcinoid was well established, but the site of the primary tumor, the location, and the extensiveness of the metastatic lesions were not identified, especially those in the liver. From information of other case reports, chiefly retrospective in nature, there was now a good explanation for the 2 prolonged episodes of fever at the ages of 17 and 35 in which disease developed about the right hemidiaphragm and in which a sterile abscess formation was surgically drained. These episodes probably represented necrosis and breakdown of metastatic nodules in the liver. Similar complications had been reported.[9] The possibilities of these nodules being in one area of the liver suggested possible surgical resection of the liver, but the patient again refused surgery, even for simple exploration. In December 1955 an episode of acute abdominal pain and features of acute intestinal obstruction developed, and it appeared that emergency surgery would be necessary; however, this condition subsided with intestinal drainage. With possible recurrence, elective surgery was again advised which she again refused, this time just prior to going to the operating room.

During the remaining period of life, from 1956 to death in 1963, she maintained a reasonable state of comfort on a program of medical management which was periodically disrupted by acute emotional and psychotic episodes during which she often entered other hospitals or sought new and unknown physicians, at times in the middle of the night. During this interval she moved with her husband to various military assignments in the United States and to one foreign assignment. In all, she was seen by a vast number of physicians. This patient was last seen by one of us (T.W.M.) in March 1963 when she was in Walter Reed General Hospital for a period of evaluation. She had developed tissue wasting like a patient with hepatic cirrhosis. The telangiectasia and cyanosis about the cheeks and forehead and legs had increased in severity, presenting a grotesque appearance. The cardiac findings remained essentially as before. An interesting finding at this point was the presence of essentially normal liver function studies after years of metastatic involvement. However, a liver scan with radioactive gold demonstrated extensive replacement of the left lobe and the upper medial portion of the right lobe. At this time the alkaline phosphatase was 10.5 King-Armstrong units. Total proteins by electrophoresis were 4.6 Gm. Several 24-hour specimens of urine resulted in 5 HIAA determinations of 147 mg., 108.5 mg. and 36.7 mg. respectively. These values were lower than those obtained in prior studies.

The management of failure and maintenance of good nutrition became an increasingly difficult problem with the development of additional pellagrous skin lesions about the hands and lower legs. The patient died in the U. S. Army Hospital at Fort Jay, N. Y. in September 1963. Some of the highlights of the autopsy findings are presented, especially as they relate to previous diagnostic problems.

Chest: The right pleural cavity was completely obliterated by dense fibrous adhesions with the right hemidiaphragm at the level of the fourth rib. The heart weighed 380 Gm. The foramen ovale was closed, and no atrial or ventricular defects were present. The right atrium and ventricle were moderately dilated, and there was slight dilatation of the left-sided chambers. The endocardium of the chambers was normal in appearance. The tricuspid valve presented great changes with thickened and retracted leaflets. The valve edges were rolled and the endocardium was opaque. The chordae were fused, thickened and shortened. The circumference measured 11 cm. The pulmonary valve measured 5.2 cm. in circumference, was thickened, retracted, and rigid. There was moderate post-stenotic dilatation of the pulmonary artery, and a few shiny plaques were present on the intimal surface. The mitral and aortic valves were grossly normal, but histologic studies revealed fibrosis. The microscopic changes in the pulmonic and tricuspid valves were similar to those described in other cases.[10] The pulmonary arteries did not show the changes of hypertension.

Abdomen: The liver was enlarged and protruded 3 fingerbreadths below the costal margin. There was 2,500 c.c. of fluid in the abdomen. A 4 cm. mass was present in the mesentery of the small bowel, which on study was identified as carcinoid tumor in a mesenteric lymph node. Initially no tumor was found in the bowel itself, but fortunately the entire bowel was saved and was sent to the Armed Forces Institute of Pathology. At that institution careful inspection revealed a carcinoid of the usual size and character in the lower ileum (figure 2). The liver was enlarged, but no masses were noted on the outer surface. On section, 90 per cent of the liver parenchyma was seen to be replaced by tumor masses or cystic areas from previously degenerated tumor nodules (figure 3). These nodules measured up to 6 cm. in diameter. The right ovary was normal, but the left was cystic. Neither had metastatic lesions.

The large cystic area on the superior and diaphragmatic surface of the liver probably represented the residual of nodular necrosis and sterile abscess formation which was drained in the subdiaphragmatic area in 1934 when the patient was 17 years of age. The other cystic area probably represented the necrosis and sterile abscess formation in the liver as observed clinically at Hopkins in 1952 when she was 37 years of age.

Summary

In this brief narration we have presented the sequential events and observations of many physicians over a period of years, finally resulting in a correct diagnosis in a very perplexing clinical problem.

The final diagnosis, including the site of the

primary tumor, was almost missed after autopsy, and only by a careful review of the autopsy material at the AFIP after accession in that institution was the primary carcinoid located in the usual ileal site.

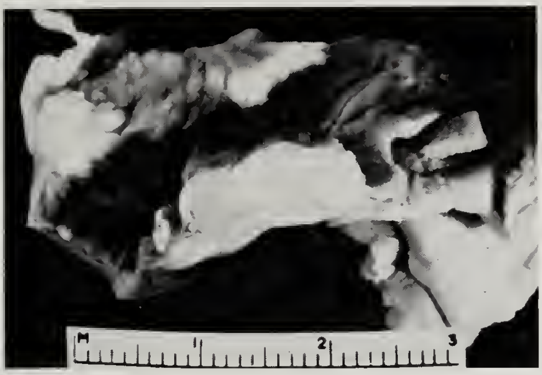

FIG. 2. Section of ileum and the carcinoid tumor. Note small size (1.5 by 1.2 cm.) of tumor which, from history, was metastatic for years. The primary tumor was overlooked during initial autopsy study and only the metastatic tumor in mesentery identified.

In retrospect, this patient over a period of 35 years presented most of the clinical features presently described in a functioning metastatic carcinoid tumor. The chronicity of this tumor after invasion and liver metastasis is again documented, this patient having had vaculocutaneous symptoms (flushing) for 35 years, definite evidence of hepatomegaly for 28 years, 2 episodes of necrotic degeneration of liver nodules—28 and 11 years, and evidence of cardiac involvement for 15 years before death.

Finally, the eventual clinical diagnosis in this patient, probably the first made in the United States, was not the result of the considerations of any one physician but a gradual accumulation of information, which, put together along with chance association with activities of others, resulted in the clinical and laboratory diagnosis. A final note of commendation must be given to the house staff at Johns Hopkins Hospital who initially detailed the symptoms and the description of the vasculocutaneous lesions in 1949 at a time when they had no idea as to what they were describing. Had the knowledge of the earlier cases been available to them, the correct diagnosis would have been suspected immediately. The delay in diagnosis in this patient illustrates the need for better systems of accumulating and communicating medical knowledge. If the information as published earlier by Scholte[11] of Holland in 1931, Cassidy[12] in England in 1934, and Feyrter[13] of Germany in 1934 had been generally known in this country, the tumor would have been recognized in 1934 when the patient was first hospitalized with flushing and hepatomegaly and subphrenic abscess. Furthermore, in 1949 when the patient was studied initially at the Johns Hopkins Hospital with the history and presence of the vasculocutaneous lesions and the cardiac lesions which were so beautifully described, simple knowledge of the case report of Millman[14] of New York in 1943 should have suggested that the hepatic disease, flushing, and heart disease were related.

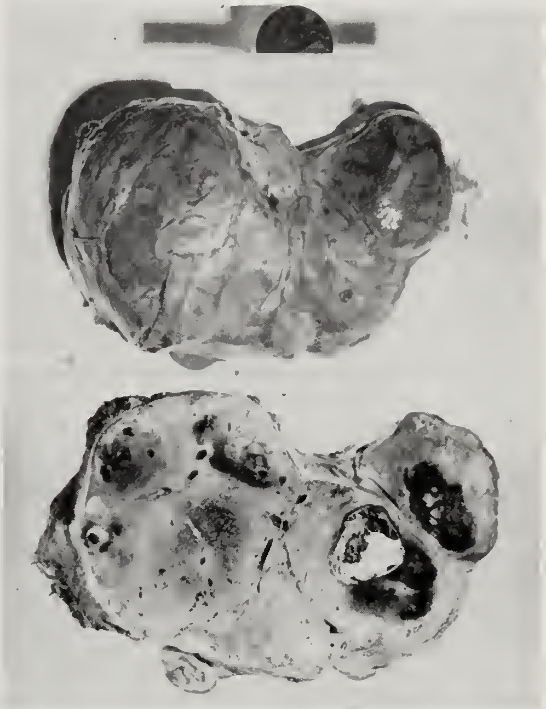

FIG. 3. Gross and cut section of liver. Note how gross appearance of liver (above) reveals but little of the extensive tumor replacement as seen on cut section (below). Cystic areas are residuals of aseptic necrosis of metastatic tumors which broke down with abscess formation at the ages of 17 and 35 years.

On the other hand, the meeting of the Second World Congress of Cardiology in Washington, D. C. in 1954, at a time when this subject was of acute interest to European physicians and the inclusion of this subject in the program of the Congress resulted in a rapid dissemination of the existing knowledge. Our presentation of this live patient to a group of clinicians and professors and the studies at the National Institutes of Health and the publications of Sjoerdsma resulted in an unusually rapid dissemination of knowledge of this clinical entity. Today every junior medical student is familiar with the entity.

Discussion

Dr. William B. Bean (Iowa City): I remember vividly seeing the patient that Dr. Mattingly has described. There are 2 points that I should like to make. The first is that although logically with this tryptophan-related problem one might expect that pellagrous skin lesions would indeed occur, I doubt that they do. I have had the opportunity to see several hundred persons with florid pellagrous skin lesions and perhaps a dozen patients with carcinoid. The lesion in carcinoid is in no way the same as the pellagraderm in spontaneously developing clinical pellagra. Although logical, I think it is an erroneous interpretation of what is more likely a verrucous skin lesion with a number of telangiectatic changes which have an utterly different histopathology from the ordinary lesions of pellagra.

The second point which perhaps Dr. Mattingly made (I did not get in for the beginning of his talk) was that the discovery of serotonin represents a negative serendipity. The physiologic force of this intense vasoconstricting agent was recognized in German laboratories about 80 years ago, when it was found that blood which had been clotted had added to it an intense vasoconstricting property which made it impossible for the people doing perfusion experiments to use blood unless they used an anticoagulant. In other words, they could not defibrinate it and use it to measure blood flow and the volume of the kidney. They found, however, that if this blood was run through the lungs of the animal and then through the kidney the vasoconstricting property was removed. Here was a fantastic pharmacologic event. All physiologists who were doing perfusion experiments were well aware of it. But it was years later that Irvine Page, looking for any vasoconstricting agent that might have some role in hypertension, discovered serotonin—because of his familiarity with its vasoconstricting property which occurs in the process of clotting, as we now know, from the serotonin unloaded from the platelets.

Dr. Lewis Dexter (Boston): This has been a beautiful historical essay on the problem presented by the carcinoid syndrome, and I must say I congratulate you, Dr. Mattingly, on this fascinating case history. I wish I could remember what I said to Allen Friedlich. To tell the truth, I don't remember anything about it. I have often wondered how Biörck happened to recognize and identify this disorder. Do you happen to know the details?

Dr. Mattingly: First, a comment about your previous statement. All we have is the information in Dr. Allan Friedlich's letter to Dr. Taussig. Perhaps it was a chance conversation between you and Dr. Eugene Eppinger in which he asked what one might do surgically with a severe tricuspid insufficiency. At that time it was not known that it was of carcinoid etiology. The question was simply one of the feasibility of surgical treatment of tricuspid valve insufficiency.

I do not know the exact details as to how Dr. Biörck and associates rediscovered the clinical carcinoid syndrome and related it to serotonin. They published the first case report in 1952, as I stated in the paper. At that time they discussed only the possibility of a causal relationship. In the next 2 years (1952 to 1954) Isler, Hedinger, Waldenström, and others reported similar cases. The key to the solution was really the unearthing (rediscovery) of some of the old information about the action of serotonin and finally the finding of serotonin in carcinoid tumors (Erspamer, 1952). In 2 years (1952–1954), when this series of observations was put together, it became apparent that there was a basis for causal relation and an explanation for the multiple clinical features. Millman, 10 years before in this country, and Scholte and Cassidy, 20 years before in Europe, had reported the occurrence of the metastatic carcinoid tumors, the flushing episodes, and the cardiac lesions occurring together in the same patient. They questioned whether there was an etiologic relationship. Therefore, it was primarily the series of events which occurred in the short time (1952–1954) which firmly established the concept of a functioning carcinoid tumor.

I agree with Dr. Bean that the usual skin changes are not those of pellagra, and I have not seen true pellagra in this condition. The skin lesions described as pellagra in this patient were described in the records by physicians who saw her between 1956 and 1963. These were secondary lesions about the wrists and legs and did not refer to the flushing and telangiectasia about the face.

Finally, another example of negative serendipity is that although these clinical observations and the study of the action of serotonin aided in the discovery of the relationship between carcinoid tumors and the clinical features of the syndrome, it has left us with just as many unknown factors. Serotonin itself, or even one of its metabolic products, probably does not produce the cardiac lesions. Today we do not know what produces the cardiac lesions and cannot reproduce them experimentally. I am sure that Dr. Sjoerdsma and his co-workers today would like to tear up much that they have written about the action of serotonin in this clinical entity because they are currently of the opinion that the concept of serotonin production of the heart lesions remains purely conjectural.

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(*Continued on page 640*)

Peritoneal Dialysis in a Community Hospital*

(Salem County Memorial Hospital)

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The introduction of practical methods of artificial dialysis, either "artificial kidney" hemodialysis[1] or intermittent peritoneal dialysis,[2] has been a major therapeutic advance. Undoubtedly many lives have been saved by these relatively simple procedures. The goal of dialysis is to restore the composition of body fluids to normal by removing dialyzable toxins, both endogenous and exogenous, and to correct abnormalities of electrolyte and water concentration. The major indications for artificial dialysis have been life-threatening, potentially reversible renal failure, certain drug and chemical poisonings, refractory pulmonary edema and anasarca, electrolyte abnormalities, and hepatic coma. In chronic uremic states due to irreversible renal parenchymal damage life can be substantially prolonged.[3-6]

Artificial kidney hemodialysis is about 4 times as rapid in its extraction rate as intermittent peritoneal dialysis. However, this advantage is to some extent offset by its greater difficulty of performance, its relatively complex and costly equipment, and its need for more specially trained personnel. The results achieved by the 2 methods are, by and large, comparable except when speed is a critical issue.[3] In some centers in which both methods are available, peritoneal dialysis is preferred because of its simplicity.[4] For the community hospital, intermittent peritoneal dialysis is by far the modality of choice. In my opinion every hospital should be capable of promptly instituting this procedure. Several staff members should be taught the relatively simple principles and techniques involved, and a stock of commercially prepared solutions, catheters, and tubing should be on hand.

Briefly stated, intermittent peritoneal dialysis involves the intraperitoneal installation of a sterile solution containing the important serum electrolytes in the same concentration as that of normal extracellular fluid, plus 1.5 per cent glucose to make the solution isotonic. Two liters are instilled into the peritoneal cavity by gravity through a plastic catheter, and after a 1- to 2-hour equilibration period the fluid is drained off by siphonage. This procedure is repeated over and over for 24 to 48 hours and then terminated. It may be restarted as often as is clinically necessary. Dialyzable substances will diffuse through the peritoneal membrane from the region of greater to that of lesser concentration until equilibration is achieved. The commercial solutions used are potassium-free, since reduction of hyperkalemia is often a major therapeutic goal. When hyperkalemia is not a problem, 4 mEq./liter of potassium should be added to the dialyzing fluid. When it is desired to extract water from the body, dialyzing solutions made hypertonic with 7 per cent glucose are used. I have generally employed the technique described by Maxwell et al.[3] However, in most instances I have not added either heparin or antibiotics to the dialysis fluid and have encountered no difficulty as a result.

In this report 5 consecutive patients treated by me with peritoneal dialysis are described. In all, dialysis effectively accomplished its purpose. Three patients are still living. One expired 1 week after successful dialysis due to an unrelated cause; another died of end-stage nephritis after 10 months of repeated intermittent dialysis. A tabulation and description of the cases follow:

Case 1. *Oliguric renal failure.* Acute tubular necrosis secondary to crush injuries and shock.

Case 2. *Oliguric renal failure.* Acute tubular necrosis secondary to diabetic coma, probable myocardial infarction and shock.

Case 3. *Oliguric renal failure.* Acute glomerulonephritis in a 12-year-old child complicated by congestive heart failure, cerebral vascular accident with hemiplegia, and massive upper gastrointestinal hemorrhage.

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Case 4. *Hepatic coma.* Cirrhosis with coma precipitated by massive esophageal hemorrhage.

Case 5. *Chronic renal failure.* Uremia due to chronic glomerulonephritis; anasarca sometimes a problem: chronic intermittent dialysis.

Case 1. A 56-year-old male laborer was admitted to the Salem County Memorial Hospital on May 4, 1960. He had been accidentally crushed between the chassis and cab of his dump truck for a 4-hour period before being found and brought to the hospital. He was weak, pale, and clammy but alert. He complained of pain in his lower extremities and impaired vision in his left eye. The past history was essentially negative.

Examination revealed sinus tachycardia of 120 and a blood pressure of 100/0. There were a laceration of the left upper eyelid and contusions of the head, contusions and extensive ecchymoses over both lower extremities, and diminished sensation in both lower extremities below the groins. All extremities could be moved. Pedal pulses were absent on the left.

The hemoglobin was 17.5 Gm and the white blood cells numbered 21,900 with 82 per cent neutrophils. The urine was clear with occasional white and red blood cells and granular casts, the specific gravity 1.020. X-ray films revealed fracture of the left orbit and malar bone and of the right transverse process of the first lumbar vertebra.

Ophthalmologic examination revealed edema of the retina as well as loss of all but light perception and laceration and ectropion of the left upper lid.

Initial therapy consisted of 500 c.c. of blood and 500 c.c. of Ringer's lactate and 1,000 c.c. 5 per cent G/W during the night of admission. By the next morning the patient's blood pressure had risen to 120/70, and warmth, sensation and normal pulsations had returned to his lower extremities. He received an additional 1,500 c.c. of 5 per cent G/W IV on the second hospital day and was also put on oral feedings. Penicillin and tetanus toxoid were given. His oral intake was poor because of nausea and was limited chiefly to water. The urinary output was very poor. By the eighth hospital day the patient was drowsy and apathetic with nausea and occasional vomiting. At this time I was asked to see the patient in consultation.

A review of the situation on May 12 revealed that severe oliguria had been present from May 4 to May 12 with an average daily output of 400 c.c. of urine. During this period the urinary output plus emesis plus insensible water loss was estimated at 12,000 c.c. The total oral and parenteral intake was about the same. The hemoglobin had fallen from 17.5 to 11 Gm. The blood urea nitrogen had risen to 260 mg., and the serum potassium was 9.2 mEq./liter. The CO_2 was 28 vol. per cent. The urine contained 1+ albumin, a few white and red blood cells and granular casts, and the specific gravity was reported as 1.027. The ECG revealed 1° A-V block, delayed I-V conduction, and tall peaked T waves consistent with hyperkalemia. The diagnosis of acute tubular necrosis with oliguric renal failure was made.

Because of severe hyperkalemia, acidosis and clinical deterioration, peritoneal dialysis was advised and was instituted on May 13. The dialysis was carried on for 65 hours, and a total of 30 2-liter exchanges was accomplished without difficulty. No heparin or antibiotic was used in the dialysis fluid. Parenteral tetracycline was given. Intravenous fluids were also administered because of severe nausea. The patient appeared noticeably more alert within 24 hours. The serum potassium fell from 9.2 mEq. to 6 mEq./liter in 12 hours and to 5.5 mEq./liter in 36 hours. The CO_2 rose from 28 to 50 vol. per cent. The BUN dropped from 260 to 100 mg. by May 16. There was some decline in urinary output during the dialysis procedure followed by a gradual increase to polyuric levels. The appended graph indicates the fluctuations in these parameters during the course of the illness. During the week after termination of the dialysis there was a secondary rise in the BUN and serum potassium to a new high of 165 mg. and 6.1 mEq./liter and then a spontaneous decline. At the time of discharge the BUN was 30 mg. per cent and serum potassium and urine normal. The patient appeared fully recovered except for loss of vision in his left eye. Recent examination of the patient reveals normal BUN and urine.

Comment. Oliguric renal failure due to crush syndrome is ideal for peritoneal dialysis. Spontaneous healing of the acute tubular necrosis is the rule if the patient does not die of the chemical consequences of excretory failure in the interim.[7] Dialysis, by normalizing the body fluid composition, can postpone death and allow time for spontaneous healing to occur. In this case dialysis probably should have been undertaken earlier. The dialysis was prolonged because of the severe chemical aberrations. I believe the procedure was life-saving.

Case 2. A 62-year-old woman was admitted to Salem County Memorial Hospital on November 10, 1964 at 10 p.m. in a comatose state. There had been a 2-week illness with thirst, polyuria, sore throat, weakness and coma. She had received antibiotics prior to admission. She was said to have been in excellent health. She had had a cholecystectomy at 53, a hysterectomy at 50, and a thyroidectomy at 52. There was no history of diabetes or cardiovascular disease.

The patient was unresponsive, restless, and thrashing about. The skin and mucous membranes were dehydrated. The pulse was 100, the blood pressure 150/70. Respiration was deep and rapid and the breath fruity. The deep tendon reflexes were decreased. The remainder of the examination was negative. A Foley catheter was inserted, and 400 c.c. of concentrated urine was obtained. This gave 4+ reactions for sugar and acetone. The blood sugar was 1,425 mg. Serum acetone was positive in 1:16 dilution. Severe diabetic acidosis was diagnosed and treatment with insulin and parenteral fluids was promptly instituted.

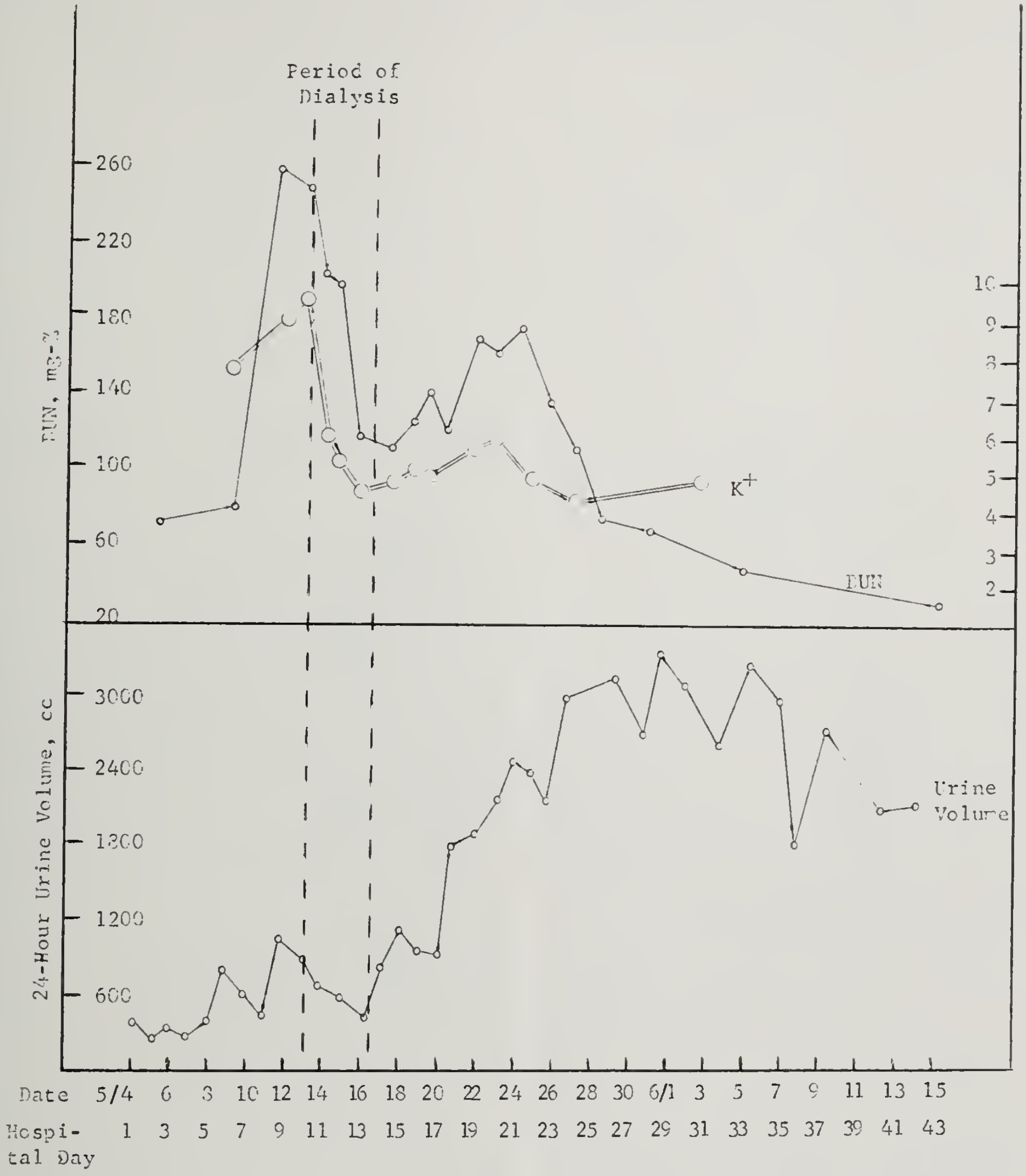

FIG. 1. Case 1. Fluctuations of BUN, K+, and urine volume during admission.

During the first 8 hours in the hospital the patient received 375 units of regular insulin and 3,000 c.c. of saline and 5 per cent glucose in saline. At this point her urine was free of acetone and the serum acetone was positive only when undiluted. The blood sugar was still very high (1,300 mg.). The BUN was 103 mg., and the CO_2 44 vol. per cent. The patient excreted only 50 c.c. of urine during this period. Despite the great improvement of her acidosis, she appeared to be deteriorating. Her blood pressure fell to 50/0, and she was in clinical shock. An ECG revealed great ST depressions in L_1, L_2, AVL, AVF, and V_3-V_6. The serum potassium was 3.7 mEq./liter.

The bed was placed on shock blocks and 500 c.c. of dextran, 80 mEq. of potassium chloride, and 500 c.c. of blood rapidly administered. The blood pressure rose nicely to 110/60 and the pulse slowed. Parenteral fluids and insulin were continued so that, after 24 hours in the hospital, the patient had received 1,000 units of regular insulin and 5,750 of fluids and electrolytes and 50 c.c. each of blood and dextran. She was then free of acidosis and the blood sugar was 145 mg. An ECG now revealed extensive deep late T-wave inversions in the limb and chest leads. Myocardial infarction was strongly suspected despite absence of diagnostic Q waves, and this could well explain the hypotension and vascular lability. Still practically no urine had been excreted. It was evident at this point that renal shutdown and cardiovascular problems had replaced diabetic acidosis as the major therapeutic challenge. On the second hospital day another hypotensive episode associated with Cheyne-Stokes respiration occurred. This responded promptly to shock blocks and intravenous aminophyllin.

After 5 days in the hospital the patient had received about 12 liters of parenteral fluids and had excreted only 600 c.c. of urine (exclusive of the urine in her bladder on admission). There was no response to 25 Gm. of intravenous mannitol. The hemoglobin was 14 Gm., potassium 4.9 mEq./liter, BUN 159 mg., CO_2 50 vol. per cent. The patient was still drowsy and too nauseated to take oral feedings. Basal rales and some dyspnea were present, suggesting cardiac failure and probably some fluid overload, and the patient was digitalized. Because of 5 days of severe oliguria, the unstable cardiovascular status with suspected myocardial infarction, and the persistent drowsiness and nausea, it was thought that peritoneal dialysis should be undertaken before further chemical deterioration occurred to jeopardize her now most precarious condition.

Peritoneal dialysis was instituted on November 15 and continued for 36 hours. Fifteen 2-liter exchanges were accomplished after 1-hour equilibration periods. No difficulty was encountered and the vital signs remained stable. No heparin or anticoagulant was added to the dialysis solution. The BUN fell from 159 mg. to 108 mg. and the potassium from 5 to 4 mEq./liter. The patient appeared brighter but was still weak. The urinary output rose to 600 c.c. on the second postdialysis day and on the third there was a 2,600 c.c. diuresis which continued for several days. Despite the diuresis there was a secondary rise in the BUN to 156 mg. by November 23, 1 week postdialysis. There was a spontaneous decline thereafter associated with gradual and progressive gain in strength and alertness. By November 30 the BUN was 28 mg. The patient's insulin requirements seemed minimal, and she was placed on 500 mg. of chlorpropamide daily, and the insulin was stopped. She had no further glycosuria, and a normal fasting blood sugar was present. A sacral decubitis ulcer was debrided and a plastic closure done. She was ambulated and discharged on December 31 with a BUN of 21 mg. and a normal urinalysis. She was doing well 11 months later, still on chlorpropamide. Her ECG was not yet normal.

Comment. A case of severe diabetic acidosis with unusually high blood sugar levels, probable myocardial infarction with hypotension, and acute oliguric renal failure has been described. Acute tubular necrosis was doubtlessly present. It was thought that the chemical consequences of more prolonged oliguria would not be tolerated, and dialysis was performed. A secondary rise in the BUN occurred, peaking 1 week after the dialysis and then receding with continuing diuresis. This secondary rise, which also occurred in the previous case, indicates that spontaneous functional recovery was not "just around the corner." It was thought that dialysis played a vital role in gaining time for spontaneous healing to occur in this critically ill patient.

Case 3. A desperately ill, 12-year-old Negro girl was admitted to my service at the Salem County Memorial Hospital on November 23, 1962 with marked dyspnea and generalized edema. She had been in excellent health until 2 weeks before admission. At that time she developed a purulent pharyngitis and received penicillin from her family physician. One week later she developed facial swelling followed by edema of her lower extremities and increasing shortness of breath. When the facial edema was first noted a penicillin reaction was suspected by her doctor and she was started on dexamethasone and Benadryl® with no benefit. One day before admission grossly bloody urine was first noted.

The temperature was 105°F, and the patient was dyspneic and orthopneic. The blood pressure was 150/120 and the pulse 156 and regular. There was edema of the face, hands, and lower extremities. The vaginal labia were painfully swollen and hung down like sacks of water between the thighs. The retinal arteries were narrowed, and a retinal sheen was present. The cervical veins were engorged even in a sitting position. Basal rales were present. The heart was enlarged and a diastolic gallop was noted. There were no rubs or murmurs. The liver edge was palpable.

Thirty c.c. of grossly bloody urine was obtained by Foley catheter. The specific gravity was 1.032, there was 4 plus albumin, and red cell casts were present. The hemoglobin was 11.9 Gm., and the white blood cells numbered 32,000 with 90 per cent neutrophils. The BUN was 40 mg. Blood and urine cultures were reported sterile. An ECG revealed low T waves. A portable chest X-ray film indicated cardiac enlargement. An antistreptolysin titer was 1,250 Todd units.

A diagnosis of acute poststreptococcal hemorrhagic glomerulonephritis with hypertension and congestive heart failure was made. Initial therapy consisted of intravenous digitalization, oxygen inhalation, and intramuscular oxytetracycline. Reserpine, 2 mg., and Apresoline®, 20 mg., were given intramuscularly every 8 hours when needed for blood pressure over 110 mm. diastolic. Steroid therapy with dexamethasone, which had been initiated prior to admission, was continued in dosage of 4 mg. every 6 hours intramuscularly. Daily fluid intake was restricted to 800 c.c. plus the volume of the urinary output, and was low in potassium. The very painful labial edema was relieved promptly by multiple scalpel punctures through which the edema fluid escaped.

On the above regimen the child improved visibly with lowering of temperature and improved respiration. She was oliguric, however, excreting 60 c.c., 95 c.c., 180 c.c., and 500 c.c. of urine successively during her first 4 hospital days. On November 26, the fourth hospital day, the BUN was 95 mg. and the CO_2 40 vol. per cent. The serum potassium was 6.4 mEq./liter despite administration of a cation exchange resin (SKF special resin). Extensive T-wave inversions were now noted in the ECG, consistent with myocarditis.

On November 27 the patient was found semicomatose with complete right hemiplegia. The neck was supple. No eyeground changes were noted. Lumbar puncture revealed normal spinal fluid and manometrics. Cerebral thrombosis, perhaps due to cerebral arteritis, was suspected. On this day the urine output was 515, the largest amount since admission. The BUN had risen to 180 mg.

With the marked hyperkalemia, azotemia, oliguria, cerebrovascular accident, and coma, the patient's condition appeared desperate. It was decided to institute peritoneal dialysis to achieve a more physiologic internal milieu to gain time for the patient to overcome her renal and cerebral lesions.

Dialysis was instituted and continued for 30 hours, during which 22-liter exchanges were performed, cycling every hour. The standard dialysis solution was employed without addition of anticoagulants or antibiotics. At the termination of this dialysis period the patient was semicomatose with the BUN 111 mg., potassium 7.2 mEq./liter, and CO_2 42 vol. per cent. The next morning the blood pressure fell to 70/0 with clinical shock present. The hemoglobin was 12 Gm., and the temperature rose to 102°F. The hypotension responded promptly to intravenous Aramine® infusion. Severe oliguria persisted. It was decided to resume dialysis through the abdominal catheter which had been left in situ.

The second dialysis, started on November 29, was continued for 40 hours, and 22 exchanges were accomplished uneventfully. When it was terminated on December 1, the BUN was 45 mg. and the potassium 4.2 mEq. per liter. The patient was alert and could take oral feedings. The urinary output on December 2 was 1,100 c.c. and on December 3, 450 c.c.

On December 4 a further complication appeared: the passage of numerous tarry and dark red bloody stools, associated with fall in hemoglobin to 6.7 Gm., blood pressure of 90/30, and clinical shock. The BUN rose to 115 mg. After transfusions of 7 units of blood by venous cutdown the hemoglobin stabilized at 12 Gm. and the patient was brought out of shock. Gastric aspiration revealed no blood in the stomach. The bleeding source was never demonstrated but was thought to be stress or steroid-induced ulceration of the small intestine. No further bleeding occurred. No disturbance in the blood clotting mechanism could be demonstrated.

After the above episode the urinary output increased to over 2,000 c.c. daily. Heavy albuminuria persisted, and the specific gravity was in the region of 1.010 with red blood cell casts persisting. The BUN gradually fell and by January 10, 1963 was 10 mg. The patient gained strength and weight. The hemiparesis and aphasia persisted, however. On January 11 the child was transferred to a rehabilitation center for intensive physiotherapy. She has improved considerably. Her urine, after a few months, became normal and has remained so. She has returned to school and is developing normally.

Comment. This child presented oliguric renal failure due to hemorrhagic glomerulonephritis. Hypertension, congestive failure, cerebral vascular accident, and massive gastrointestinal hemorrhage were complications. Peritoneal dialysis was performed twice. There seems little doubt that it played a major role in permitting her survival and recovery.

Case 4. This patient, a man aged 43 years, was kept alive for 10 months with repeated peritoneal dialysis. He was first seen by me on June 5, 1962 when he was admitted with a 5-day history of hematemesis and melena and a hemoglobin of 3.5 Gm. There was no history of gastrointestinal disease, hypertension, or kidney disorder. There was no pain. There was a history of rheumatoid arthritis, chiefly of the hands, for which the patient took considerable aspirin. He was pale, and his blood pressure was 160/90 and the pulse rate 120. There was grade 3 hypertensive retinopathy. The chest and abdomen were negative. Tarry stools were present. The BUN was 105 mg., and there was 2 plus albuminuria. The specific gravity of the urine was 1.015. The patient received 9 pints of blood, and the hemoglobin stabilized at 12 Gm. He was never in clinical shock and had a daily urinary output of over 2,000 c.c. The BUN fell to 78 mg. An ECG showed left ventricular hypertrophy. A chest X-ray film was negative. A gastrointestinal X-ray examination was negative except for a small sliding hiatal hernia. Cystoscopy was negative. Retrograde urography revealed reduplication of the right ureter and a bifid pelvis on the right. There was no suggestion of obstructive uropathy.

The blood pressure was lowered to 160/100 with methyldopa and Apresoline at the time of discharge.

The cause of the massive hemorrhage was not clearly established on this admission. It was believed that the patient had chronic renal parenchymal disease, probably chronic glomerulonephritis, with moderately advanced renal failure, in a polyuric stage.

The patient was seen several times in the following months and felt well. He failed to reappear until 9 months later when he was seen with headache, vomiting, and a blood pressure of 240/130. He was readmitted to Salem County Memorial Hospital. His BUN was 90 mg., creatinine 5.4 mg., hemoglobin 14 Gm., and albuminuria 2 plus. The blood pressure was brought to 130/90 on bedrest and methyldopa, reserpine, and Apresoline. The urinary output was high. The BUN did not improve. He was discharged on the above medication and a diet low in protein. He returned to work on this program and felt relatively well despite polyuria, nocturia, and a BUN between 70 and 90 mg. He was readmitted to the hospital on August 29, 1964 because of a vesicular rash of the hands and a blood pressure of 240/130. The fundi were grade 2, the BUN 132, and the creatinine 9 mg. The serum potassium was 5.2 mg. and the hemoglobin 11 Gm. Again the blood pressure fell to 150/90 with antihypertensives and rest, and the rash was cleared with oral prednisone.

On October 16, 1964 the patient was readmitted because of vomiting, diarrhea, weakness and dehydration. The blood pressure was 220/130, the fundi grade 3, and the BUN 180 mg. Two episodes of convulsions and transient unconsciousness occurred. The basically hopeless prognosis of this patient had long been recognized, and death due to uremia seemed inevitable. The possibility of long-term peritoneal dialysis was considered, and on this occasion it was decided to embark on such a program, after discussing the prognosis with his wife. A plastic cannula had been obtained through the courtesy of Colonel K. Barry of Walter Reed General Hospital. This cannula can be left in situ leading into the peritoneal cavity and repeated dialyses done through catheters passed into the abdomen through this cannula. Dialysis was undertaken, and the BUN came down to 72 mg. after 25 exchanges. The patient's clinical improvement was great. He was discharged on methyldopa, 750 mg. q.i.d. on October 28, 1964.

The patient was followed closely thereafter and readmitted to the hospital 12 more times for repeated peritoneal dialysis at intervals of 2 to 4 weeks, depending on his clinical condition. His uremic manifestations could always be brought under control by dialysis, and he would be discharged much improved. After about 2 weeks or so anorexia and vomiting would lead to readmission. Anemia required frequent transfusions. In March 1965 severe anasarca became a complication and dialysis with dialysis solution containing 7 per cent glucose was employed. The patient was relieved of 10 liters of edema fluid in 24 hours by this technique.

As the disease progressed the polyuria gave way to oliguria, and the periods of relative comfort between dialyses gradually became shorter, so that he felt well for only a few days at a time. He had increasing dyspnea due to progressive heart failure. It was decided that continuation of dialysis was no longer justified. The last admission was August 1965 when he was admitted with a BUN of 270 mg. and potassium of 9 mEq. He lapsed into coma and died 3 days later. Autopsy revealed the small contracted kidneys of chronic glomerulonephritis. A bifid right renal pelvis and ureter were noted. A few renal retention cysts were present. Some fibrous adhesions were present in the lower abdominal cavity. A small, thick, localized collection of pus was present in the right pelvis. The heart was markedly enlarged.

Comment. In this patient repeated dialyses were easily carried out for 10 months. The plastic cannula had to be changed only once. This was because of excessive pinching of the cannula by its retention clamp. On one occasion subcutaneous infection about the catheter opening was noted, and this responded well to hot compresses and antibiotics. The purulent collection noted at autopsy was asymptomatic and unrecognized in vivo. Dialysis was finally discontinued when it became evident that comfortable existence could no longer be achieved.

Case 5. A 55-year-old white woman, a long-standing alcoholic with previously diagnosed portal cirrhosis, was admitted to my service at the Salem County Memorial Hospital on January 17, 1960 because of hematemesis which had started the evening prior to admission. She had been treated 2 years earlier for epistaxis and bleeding hemorrhoids, attributed to hypoprothrombinemia and portal cirrhosis. There was no evident precipitating cause of the present hemorrhage.

On the day of admission the patient appeared alert, warm and dry. There was mild icterus of the skin and sclerae. The pulse was 100 and the blood pressure 110/60. Numerous small spider angiomata were noted on her face, chest and neck. The heart and lungs were negative. The liver was enlarged almost to level of iliac crest and was firm and nontender. The spleen was palpable 4 cm. below the left costal margin. Hemorrhoids were present. There was no edema or ascites.

The hemoglobin was 8.4 Gm., the BUN 29 mg., the bilirubin 4.9 mg., the prothrombin time 36 per cent, the serum electrolytes normal, and the urine negative.

After being admitted the patient vomited red blood several times. The hemoglobin dropped to 8 Gm. despite 1,000 c.c. of blood. She became restless and sweaty. A Sengstaken tube was inserted and expanded and traction maintained on it. Considerable fresh blood was initially aspirated from the stomach. Shortly thereafter the bleeding appeared arrested and only small amounts of coffee-grounds material could be aspirated from the stomach.

By 9 a.m. the next morning, January 8, the hemoglobin was 10.8 Gm., and there appeared to be no active bleeding. The patient, however, was quite drowsy. Magnesium citrate was given through the gastric tube to evacuate the blood. This was followed by neomycin, 1 Gm. every 4 hours via the tube. By 4 p.m., however, the patient was in coma and unresponsive. Pupillary and corneal reflexes were present; the head and eyes were turned to the right. The neck was stiff. The deep tendon reflexes were hyperactive, and bilateral Babinski signs were noted. It was thought that the patient was in hepatic coma, although the possibility of cerebral hemorrhage also was considered. A spinal tap revealed clear fluid with no increase in cells or protein. It was thought that hepatic coma was fairly well established and was deep. It was decided to institute peritoneal dialysis with the hope of ridding the body of those noxious substances which may exist as the cause of hepatic coma.

Peritoneal dialysis was instituted on January 8 at 8 p.m. and terminated 28 hours later. Seventeen exchanges of 2 liters each were accomplished. The fluid was allowed to remain within the abdomen 1 hour before being removed. No significant difficulty was encountered with the dialysis. To each liter of dialysis solution 4 mEq. of KCl was added, since it was not desired to deplete the serum potassium. The patient received intravenous glucose and electrolytes and further transfusions during the procedure. She also received dexamethasone, 4 mg. every 4 hours intramuscularly. Within 24 hours the patient had regained consciousness and responded partially to commands. In 36 hours she was alert and able to sit up and converse and to take oral feedings. The Sengstaken tube was removed. She was placed on a low-protein, high-carbohydrate, pureed diet. Further transfusions were administered when her hemoglobin fell to 7.8 Gm. on January 14. She had no further vomiting or melena. Her prothrombin time remained low at 35 per cent with no benefit from vitamin K_1. The SGOT was 30 units and the cephalin flocculation test 3+ in 48 hours.

The improvement in the patient's mental and physical status was extremely dramatic. A portacaval shunt to prevent further hemorrhage was considered. It was hoped that the patient's nutrition and general condition and particularly her prothrombin time could be improved before undertaking this operation. However, this was never accomplished. On January 18 she suddenly had a massive hematemesis and died in 40 minutes despite our best efforts.

Autopsy confirmed the presence of severe portal cirrhosis with large bleeding esophageal varices.

Comment. The nature of the toxic substances responsible for hepatic coma has not been completely defined, but ammonia and other metabolites have been suspect. Ammonia is known to be dialyzable. Dialysis was undertaken to remove these substances if possible. There was dramatic emergence from coma following the procedure. To what degree this was due to dialysis or the other therapeutic measures employed is not certain, but dialysis may well have played a critical part, as has been reported by others.

Discussion and Summary

The cases described illustrate many of the important indications for peritoneal dialysis. Case 1 presented a straightforward problem in which acute tubular necrosis and oliguric renal failure are precipitated by severe trauma and associated disturbance in renal blood flow. The increased tissue breakdown and catabolism enhance the hazard of potassium intoxication. The renal lesion is reversible if the patient can survive long enough for healing to occur.

In Case 2 acute tubular necrosis was secondary to a more complex medical illness, diabetic acidosis and myocardial infarction, with impaired renal blood flow due to hemoconcentration and diminished cardiac output. Again the renal lesion is potentially reversible. The therapeutic problems are much more complex in this case because 3 potentially lethal illnesses are being dealt with simultaneously.

Case 3 is an instance of oliguric renal failure due to hemorrhagic glomerulonephritis. The prognosis of such a patient with severe oliguria of over 48 hours' duration is very poor, although an occasional patient has recovered following dialysis. The recovery of this child was especially gratifying considering the associated severe complications of congestive failure, cerebral vascular accident, and massive gastrointestinal hemorrhage. Two periods of dialysis were required in this instance.

Case 4 presents the problem of chronic renal failure due to chronic glomerulonephritis. In this patient we are not dealing with reversible renal lesions but with temporarily reversible chemical changes. We also had occasion in this case to relieve massive anasarca, extracting over 20 pounds of edema fluid in 1 dialysis. All we can do in such cases is to prolong life by frequent repetition of dialysis. This has been facilitated by the development of a plastic cannula which is left in situ and utilized repeatedly, thus avoiding the need for repeated trocar punctures.[6, 8] The patient had 12 dialyses performed over a 10-month period. He slowly deteriorated and passed from a polyuric to an oliguric phase of his disease, requiring more frequent dialysis to be maintained. Because he had been ambulatory throughout his illness, was in no great physical distress, was of stoic nature and seemed to have no great mental anguish, and because the procedures could be done without impoverishing his family, I was willing to continue the therapy until finally it appeared to be of little true value. At best it is an unsatisfactory approach to the problem of chronic renal failure and a poor substitute for a more definitive therapy such as successful renal transplant. The associated ethical problems are quite evident and have been much discussed.[9]

Case 5 demonstrates the application of peritoneal dialysis to remove the toxins of hepatic coma. Where hepatic coma is entirely due to increasing decline of hepatocellular function in advanced cirrhosis, only a brief respite can be anticipated at best. However, in the patient with fairly well-compensated though advanced hepatic disease in whom some acute insult (such as hemorrhage, infection, or ill-advised drug therapy) precipitates hepatic coma, dialysis is justified with hope of restoring the status quo ante. The value of dialysis in hepatic coma has not yet been widely accepted, though evidence for its efficacy has been put forth.[10]

Although dialysis can be a life-saving adjunct in the management of certain critical illnesses, it remains only a part of the total regimen. The patients so treated generally have multiple and complex problems requiring use of many therapeutic modalities, as the presented cases illustrate.

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Studies in Sickle-cell Anemia

XXXI. Preliminary Observations on the Use of Indomethacin in the Treatment of Thrombotic Crises*

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THIS REPORT deals with the effectiveness of indomethacin in the treatment of thrombotic crises due to sickle-cell anemia (SCA). Indomethacin, a new nonsteroid, anti-inflammatory and antipyretic drug, has been used in the long-term management of arthritic conditions such as rheumatoid arthritis and osteoarthritis. Beneficial effects have been reported by many workers when this drug was used in the treatment of various musculoskeletal disorders.[1-5]

Numerous agents have been employed by various routes of administration in search of a more effective method of treatment for sickle-cell thrombotic crises.[6-9] This study was undertaken to evaluate the effectiveness of indomethacin in relieving the pain, fever, and swelling of soft tissues associated with thrombotic crises.

Materials and Methods

The patients studied were infants and children who had been diagnosed as having homozygous sickle-cell disease. An attempt was made to include those whose painful crises had been observed on previous occasions and whose level of response to the usual analgesics was well known by both parents and physician.

On admission, routine history, physical examination and laboratory data were obtained. Initial blood assessment included hematocrit, hemoglobin, reticulocyte and white blood cell counts. Particular note was made of the degree of fever, location and severity of pain, and the amount of swelling.

It was decided that patients would be treated for a minimum of 48 hours before discontinuing the drug. During this period of study oral fluids would be administered as desired by the patient with no effort to force intake. Blood transfusions, intravenous fluids, and other methods of therapy were withheld during this period.

Before beginning therapy with indomethacin all medications were withheld for a 12-hour period. An oral suspension of indomethacin was administered orally every 8 hours in dosage of 1 mg. per Kg. of body weight. The rectal temperature and pain response were noted and recorded 2, 4 and 8 hours following the initial dose. Beginning 8 hours after the initial intake of the drug, records were made of the temperature and pain response at 4-hour intervals for at least 48 hours. The pain response was rated as none, very mild, mild, moderate, severe, and very severe. The ratings were all made by the same physician in order to standardize the assessment of the pain response.

Results

Six patients with homozygous SS disease‖ who manifested joint and/or soft tissue swelling characteristic of a thrombotic crisis were included in this study (table 1). The patients varied in age from 18 months to 13½ years. All experienced painful swollen joints and/or extremities for 24 to 96 hours before admission to the hospital. Low-grade fever was present in each case. Prior to hospitalization no relief was experienced on a regimen of oral fluids, analgesics, and/or steroids.

Relief of pain associated with the crisis was the first response noted. This occurred 2 to 8 hours following the first oral dose of the drug. This was followed by increased mobility and decreased swelling of the extremity. This response

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‖ Diagnosis confirmed by paper electrophoresis of hemoglobin hemolysate.

TABLE 1: Summary of Pertinent Clinical and Laboratory Data

SUBJECTS				SYMPTOMS			HEMOGRAM Admission over discharge				DOSAGE AND RESULTS	
No.	Patient	Age (yrs.)	Sex	Location of Pain and/or Swelling	Degree of Pain	Temperature Initial	Hemoglobin (Gm.)	HCT. (%)	Reticulocytes (%)	W.B.C. cu./mm.	Dosage of Drug (q. 8 h.)	Time Required for Complete Relief of Symptoms
1	A.W.	11	M	Elbow joints	Severe	99.4°F	6.2 6.4	22 24	14.6 12.2	22,950 14,400	30 mg.	72 hrs.
2	E.J.	8-$^{11}/_{12}$	M	Left elbow and arm	Severe to very severe	101.8°F	7.6 6.5	26 21	10.1 6.4	31,150 12,550	30 mg.	72 hrs.
3	E.P.	6	M	Left knee and thigh, right elbow	Severe	100°F	6.25 6.25	25 18	6.2 4.4	26,000 12,800	15 mg.	72 hrs.
4	C.R.	13-$^{6}/_{12}$	F	Left knee	Very severe	99.6°F	8.2 7.8	25 26	4.8 4.8	13,000 8,400	50 mg.	48 hrs.
5	J.N.	1-$^{6}/_{12}$	M	Hands and feet	Severe	100.8°F	5.1 5.3	20 20	— 5.8	41,250 14,600	12.5 mg.	96 hrs.
6	T.P.	1-$^{9}/_{12}$	M	Fingers of both hands—"hand-foot syndrome"	Severe	100.4°F	7.2 6.8	27 22	8.1 4.3	25,100 14,800	12 mg.	7 days

was noted 6 to 12 hours after the initial dose. The time required for complete relief of pain, joint immobility and soft tissue swelling ranged from 24 to 96 hours following initiation of treatment. The drug was discontinued after complete relief of symptoms. Only 1 patient required repeated treatment following a relapse which occurred 5 days after the drug was discontinued.

Side-effects reported in adults, such as vomiting, epigastric pain, vertigo, lacrimation, etc. were not observed in these patients.

The following case is representative of the results obtained in this study.

E.J., a Negro boy aged 8 years, 11 months, was admitted on March 16, 1965 for fever and severe pain in the left elbow of 5 days' duration. There was also swelling of the left elbow and the left arm of about 2 days' duration (figure 1). He had received 0.3 Gm. of aspirin several times daily without relief. The diagnosis of sickle-cell anemia was first made when he was 1 year old. He had been hospitalized 3 times for painful joints.

He was obviously in distress because of pain in the left elbow. His nutrition was poor. The weight was 60 lbs. 8 oz.; the height 50¾ inches; the rectal temperature 101.8°F, the pulse rate 120/min., and the respiratory rate 24/min. The mucous membranes of the

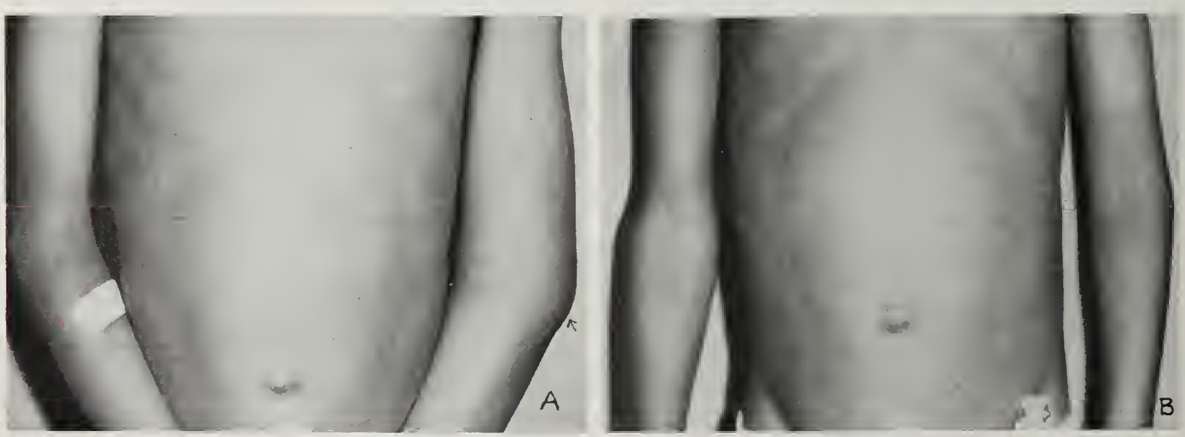

FIG. 1. Patient E. J.—A, showing soft tissue swelling in region of left elbow. The arm and forearm are held in partial flexion due to pain and tenderness; B, showing almost complete disappearance of swelling after indomethacin therapy. The arm can now be fully extended at the elbow.

mouth and conjunctivae were pale. A grade I soft systolic murmur was audible at the base of the heart. The liver was 4 cm. below the right costal margin. The upper one-third of the left forearm, the left elbow joint, and the lower two-thirds of the left arm were swollen, warm, and very painful on active and passive movements. The other joints and limbs were normal.

The urine was normal except for a specific gravity of 1.010. The hemoglobin electrophoretic pattern was SS and the fetal hemoglobin 6.4 per cent. The roentgenogram of affected parts showed no evidence of osseous involvement. The blood electrolytes were normal. The antistreptolysin titer was not unusual.

Serial hemograms showed:

Date	Hgb. Gm.	HCT. %	Reticulocytes %	R.B.C. million/ cu. mm.	W.B.C./ cu. mm.
3-16-65	7.65	26	10.1	2.56	31,150
3-17-65	6.7	25	11.4	2.48	27,000
3-18-65	6.55	23	12.3	2.26	15,200
3-22-65	6.5	21	6.4	2.17	12,550

Indomethacin was started in dosage of 30 mg. every 8 hours. Within 2 hours the child seemed to feel better. After 8 hours he was afebrile and was much more comfortable. Twenty-four hours after administration of the drug, movements were possible in the left elbow. Seventy-two hours after onset of therapy he was symptom-free and was discharged on March 22 in good condition.

Comment

The children in this series presented what was interpreted as the "thrombotic," "symptomatic," or "pain" type of crisis. This variety is characterized by the presence of pain with or without associated swelling of soft tissues. The pain and localized arthritis-like manifestations exhibited by these patients were attributed to erythrostasis, hypoxia, vasodilatation, and perivascular edema. The reversibility is shown by the disappearance of pain and local swelling and the return of the extremity to natural appearance and normal function.

In the presence of fever, leukocytosis, pain, local swelling and tenderness in the region of joints, septic arthritis and acute osteomyelitis have to be considered and excluded by appropriate studies. Rheumatic fever also has to be included in the differential diagnosis, particularly in patients with cardiac enlargement and murmurs.

It was our impression that indomethacin was more effective than other commonly used analgesics such as acetylsalicylic acid, codeine, Darvon®, etc. for the treatment of painful swellings about the joints. In addition to its anti-inflammatory, antipyretic and analgesic properties, indomethacin has been demonstrated to have a steroid-sparing effect in the human subject.[10] We usually observed some relief from pain and tenderness within 2 to 3 hours after oral administration of the drug. Hart et al[10] have shown by radioactive tracer studies that the agent is completely absorbed after 1 hour following oral administration.

The number of cases and the circumstances of the study did not permit a double-blind evaluation of the therapeutic agent in this preliminary study. However, we did have the benefit of the following observations:

1. Painful and tender swellings afforded objective evidence of their presence and disappearance.
2. Parents and physicians had witnessed the failures of other commonly used analgesics in most of these cases before the new drug was employed.
3. In the past, patients whom we had observed with similar complications due to SCA, prior to the availability of this drug, required a considerably longer time for subsidence of symptoms.

Further experience with this drug will be needed in order to determine whether it is a suitable replacement for older analgesics for the relief of pain and soft tissue swelling associated with the thrombotic crises of SCA. The drug was well tolerated by our patients and we observed no significant untoward side-effects. Other observers[11] have noted nausea and vomiting, headaches, dizziness, lacrimation, peptic ulcer, epistaxis, etc. when the drug was used for longer periods of time.

Summary

Indomethacin was administered orally to 6 children who exhibited pain and/or local joint swelling due to sickle cell-crisis.*

In our experience the drug was more effective than commonly used analgesics in the control of pain and/or local soft-tissue swelling.

The medication was well tolerated and we observed no untoward side-effects.

The authors acknowledge the technical assistance of Miss Mary E. Allen and Mr. James A. Ross of the Pediatric Research Laboratory. The indomethacin (Indocin) was supplied through the courtesy of Dr. Joseph T. Ichter and Dr. Albert L. Lamp of the Research Laboratories of Merck Sharp & Dohme, West Point, Pa.

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* Since this manuscript was prepared, 4 additional cases have been treated with salutary results.

(Continued on page 640)

Hunter-Hurler Syndrome: Clinical and Biochemical Study

Combined Clinical Staff Conference at the National Institutes of Health

ANATOLE DEKABAN, M.D., PH.D.*, OWEN RENNERT, M.D.*, AND BETTY HATHAWAY, M.D.†

The Syndrome

DR. ANATOLE DEKABAN: There are several heritable metabolic syndromes which owe their name to the excessive storage of specific compounds in various body organs. Notable examples of such disorders are lipidoses, glycogen storage diseases, and mucopolysaccharidoses. The last category of diseases has been least studied. In 1917 Hunter[1] described 2 brothers afflicted with dwarfism, hepatosplenomegaly, skeletal deformities, coarse facial features, and mental retardation. Hurler[2] in 1920 described several unrelated children with similar clinical features who in addition had corneal opacities. Most publications during subsequent years were descriptive, and several other names for this syndrome were proposed; among the more popular terms used are dysostosis multiplex, gargoylism, and lipochondrodystrophy.[3-7]

An important milestone in the study of this syndrome was the demonstration by Brante[8] that the stored material in the Hunter-Hurler syndrome is acid mucopolysaccharide (AMPS). Shortly thereafter, Dorfman and Lorincz[9] showed that affected patients excrete excesses of AMPS in their urine. Meyer et al[10] separated AMPS stored in organs and excreted in urine of these patients into its main constituents: chondroitin sulfate B and heparitin sulfate. During the past several years additional clinical and biochemical data have been accumulated, but the etiology and pathogenesis of the syndrome are still unknown. Recently, numerous attempts were made[11, 12, 13] to classify the Hunter-Hurler syndrome into several subgroups depending on the clinical features, course of the disease, type of inheritance, and the ratio of excreted mucopolysaccharides. Although none of these classifications is likely to be permanent, some of them serve a useful purpose by suggesting additional studies.

For the present there are only 3 or possibly 4 variants of the syndrome which can be considered as established: (1) autosomal recessive with about equal excretion of chondroitin sulfate B and heparitin sulfate, (2) autosomal recessive with predominant (90–95 per cent) excretion of heparitin sulfate, (3) sex-linked variant with mixed excretion of chondroitin sulfate B and heparitin sulfate, and (4) not definitely established, excretors of predominantly chondroitin sulfate B (over 90 per cent). Clinically, patients with the sex-linked variant have similar manifestations as the mixed excretors of autosomal recessive type, except that the corneal opacity is more common in the latter. The patients excreting heparitin sulfate predominantly have little skeletal changes, less abnormality of facial structures, and less frequent corneal opacities; however, they exhibit great mental retardation and the early onset of deafness. There are only a few patients described who were considered to be chondroitin sulfate B excretors exclusively.[9, 12] Certain authors[14] consider that some patients described under the eponym of Scheie disease[15] may also fall into this category. These patients usually have corneal opacities but relatively little mental impairment and absence of skeletal abnormality.

Among other disorders which are characterized by excessive excretion of AMPS are Morquio's disease, mastocytosis, and Marfan's disease. The chemical composition of various mucopolysaccharides is given in table 1.

In this conference we are concerned with the Hunter-Hurler patients, whether of sex-linked or recessive type of inheritance, who excrete a mixture of about equal parts of chondroitin sulfate

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B and heparitin sulfate or one of these compounds predominantly (over 90 per cent).

TABLE 1: Chemical Composition of Various Mucopolysaccharides

	Hexosamine	Hexuronic Acid	Sulfate
Chondroitin sulfate B (skin, tendons)	N-acetylgalactosamine	L-iduronic acid	+
Heparitin sulfate (aorta)	N-acetylglucosamine	D-glucuronic acid	+
Keratosulfate (cornea, cartilage)	N-acetylglucosamine	—	+
Chondroitin sulfate A & C (cartilage, cornea)	N-acetylgalactosamine	D-glucuronic acid	+
Hyaluronic acid (synovial fluid)	N-acetylglucosamine	D-glucuronic acid	—
Chondroitin (cornea)	N-acetylgalactosamine	D-glucuronic acid	—

Life History of Patients

Dr. Owen Rennert: It appears from the literature that the clinical and biochemical course of the Hunter-Hurler syndrome remains unclearly defined. If one refers to the Index Medicus, this disease is cataloged as a lipochondrodystrophy, when in fact it is neither a disease of lipids nor a chondrodystrophy.

Children afflicted with this disease usually develop normally for the first 6 months of life. Sometime between the ages of 6 months to 2 years stigmata of abnormal development become apparent. Most frequently such patients initially show persistent umbilical hernia, hepatomegaly and/or splenomegaly, and coarse facial features. Often an early finding is the reversal of the normal lumbar lordosis, first noted by the parents when the child is able to sit.

With the passage of years the excessive deposition of AMPS results in the classical deformities of this syndrome. Many patients develop enlargement of the head with great bulging of the squamous portion of the temporal and frontal bones and scaphocephaly (figure 1). The eyes become widely spaced. A broad nose with a flattened bridge and continually opened mouth with broad tongue and thick lips add to the grotesque facial features. This deformed head sits upon a rather short neck. The chest is usually somewhat broad but is otherwise grossly unremarkable. The abdomen is protuberant, frequently with a bulging large umbilical hernia. The extremities appear short in relation to the trunk and are usually kept in a semiflexed position. The

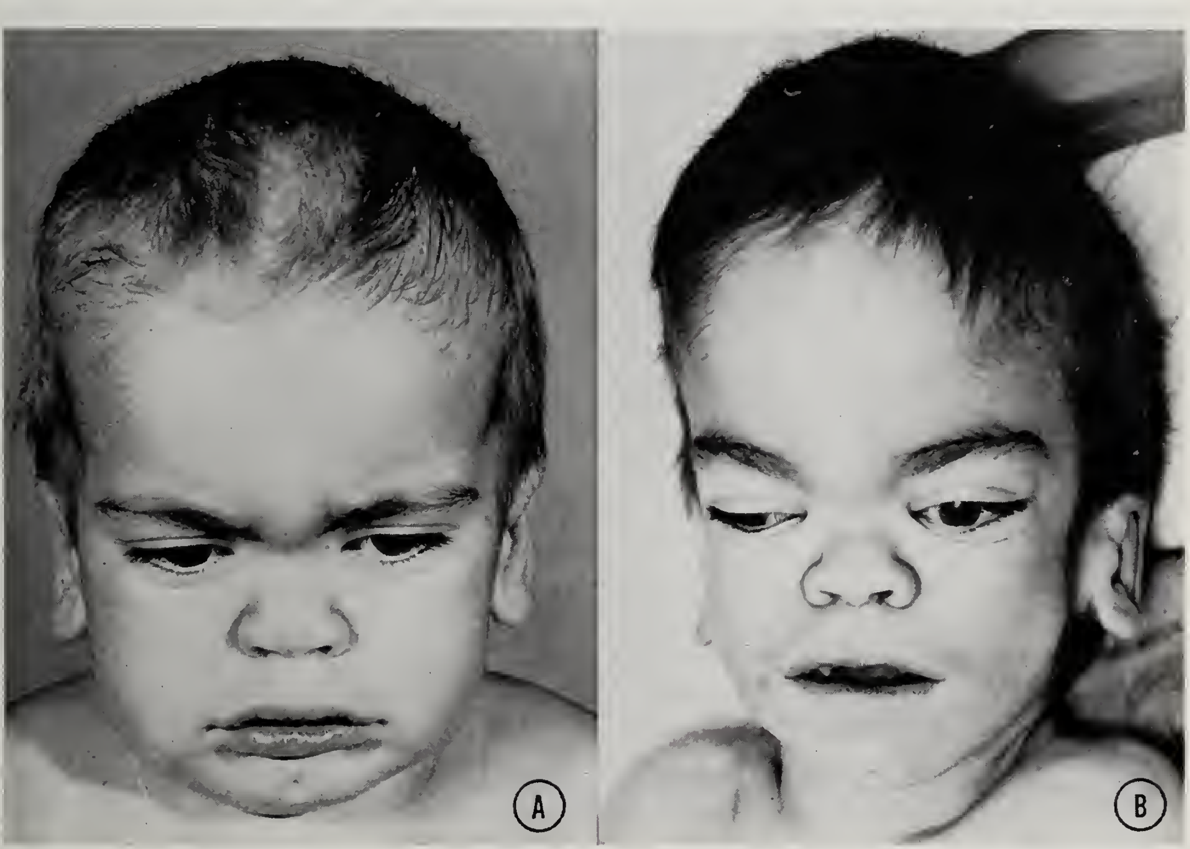

FIG. 1. Patient P. H. A, at 22 months, and B, at 7 years of age. Note change in configuration of the head and sunken bridge of nose (magnification of the prints differs).

hands are broad and stubby and may frequently appear clawlike.

Illustrative of the natural history of this disease is patient P.H., who at 3 months of age was noted to have a mild thoracolumbar gibbus, but not until 13 months of age was a diagnosis of the syndrome made. Subsequently he developed corneal clouding, protruding abdomen, and deformities of the skeletal system. Some of these findings are demonstrated in figure 1. At 7 years of age his head was enlarged and he exhibited cachexia and oblivion to his environment. Most patients with this syndrome expire by adolescence or earlier.

The cardinal laboratory finding in this disorder is excessive excretion of urinary AMPS. There are 2 simple and probably most reliable tests, the acid albumin technique of Dorfman[9] and the demonstration of toluidine blue inclusions in urinary sediment. Conclusive demonstration of this anomaly is carried out by the qualitative and quantitative isolation of AMPS by precipitation with quaternary ammonium salts and the identification of these components by chromatography or electrophoresis, and an ancillary laboratory finding is the demonstration of metachromatic inclusions in the lymphocytes.[16]

Recognition of the heterozygote is important from the genetic point of view. Thus far there has been no demonstration of increased excretion of urinary mucopolysaccharides in parents or siblings of affected children. A recent report by Danes et al[17] suggests that fibroblast tissue cultures from patients and their parents show a quantitative increase in the number of metachromatic granules over normal controls. This may be the first demonstration of heterozygote carriers.

Radiographic Demonstration of the Progression of Bony Abnormalities

DR. BETTY HATHAWAY: There are a number of radiographically demonstrable osseous abnormalities characteristic of the syndrome. These abnormalities usually are seen by the age of 12 months but may be evident at a few months of age, or they may not be apparent for 3 or 4 years.

The characteristic bony abnormalities include the following:

Skull and spine:
  a. Larger than normal and dolichocephalic in shape
  b. J-shaped sella
  c. Poorly developed mastoid processes and nonaerated sphenoid sinus
  *d. Posterior dislocation of a lumbar vertebra, usually the second or third narrow A-P diameter of the body, anterior inferior beaking, and concave posterior margin

Facial bones:
  a. Shallow orbits and prominent supraorbital ridges
  *b. Flat or concave condyloid process of the mandible
  c. Hypertelorism

Thorax and pelvis:
  *a. Broad rib bodies, sharply tapered at the vertebral extremity
  *b. Broad clavicles medially
  c. Hypoplastic ilia and transverse acetabula

Extremities:
  *a. Short humerus with broad shaft proximal and tapering distally; dorsal angulation of surgical neck
  b. Coxa plana, coxa valga, and occasional narrow proximal shaft of the femurs; genu valgum
  c. Broad metacarpals distally and tapered proximally except the first, which is broad proximally
  d. Angulation of the distal ends of the ulna and radius

Some or all of the characteristic findings may be present in any given patient. Certain of the abnormalities, when evident, are specific for this syndrome (designated by an asterisk).

In the evolution of the disease some changes may be more recognizably abnormal at an earlier age than others. Posterior dislocation of one of the lumbar vertebrae, usually L_2 or L_3, and associated deformity of the vertebral body in the form of anterior inferior beaking are frequently recognized as abnormal at an earlier period than other changes. This is seen in figure 2a, in which the posterior dislocation of L_1 and slight deformity are apparent at the age of 5 months, at which time all other X-ray studies in this child were normal. This finding is generally thought to be specific for the syndrome.

There appears to be no characteristic order of appearance of the various body abnormalities. More commonly, the changes occur simultaneously and progress at about the same pace. Sharply tapered vertebral extremities of the ribs usually are not apparent until other bone abnormalities are advanced. The rib deformities have been described as baseball-bat ribs, boat oars, and spatulate ribs. The flat or concave condyloid process of the mandible has been described as a diagnostic feature by Horrigan et al.[18] This deformity was frequently seen in our cases.

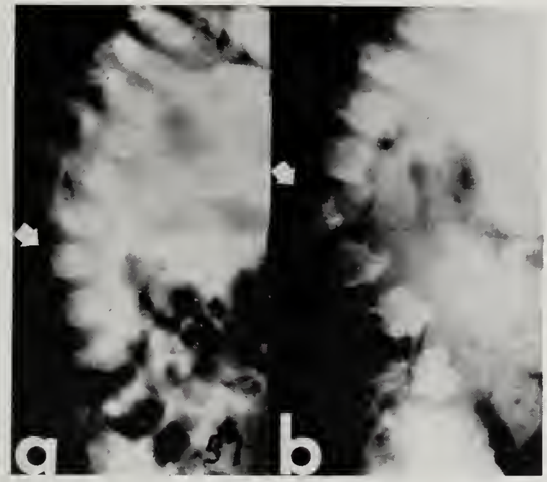

FIG. 2. Spine of a mixed excretor of AMPS. (a) Posterior dislocation of L_1 with some degree of anterior inferior beaking, and slight deformity of L_2 at age of 5 months. (b) Same patient at age of 8 years, showing an increase in degree of posterior dislocation of L_1 and in previous deformities of L_1 and L_2.

Similarly as Maroteaux and Lamy,[12] we have observed a striking difference between the skeletal abnormalities demonstrated in the patients who excrete about equal parts of chondroitin sulfate B and heparitin sulfate and those who excrete predominantly heparitin sulfate. At advanced stages of the disease the mixed excretors (CSB and HS) have great osseous changes, whereas the patients excreting predominantly heparitin sulfate have mild abnormalities. Figure 3-A illustrates irregular epiphyses, distally broad and proximally tapered metacarpals, and great radial angulation of the ulna in an 8-year-old mixed excretor. For comparison, figure 3-B shows the wrists and hands of a predominant heparitin sulfate excretor at the age of 5 years with the bony structures appearing quite normal despite the advanced stage of the disease.

The differential diagnostic considerations from a radiographic standpoint include Morquio's disease and achondroplasia. An occasional patient presents typical roentgen features of both Morquio's and Hunter-Hurler's syndrome as reported

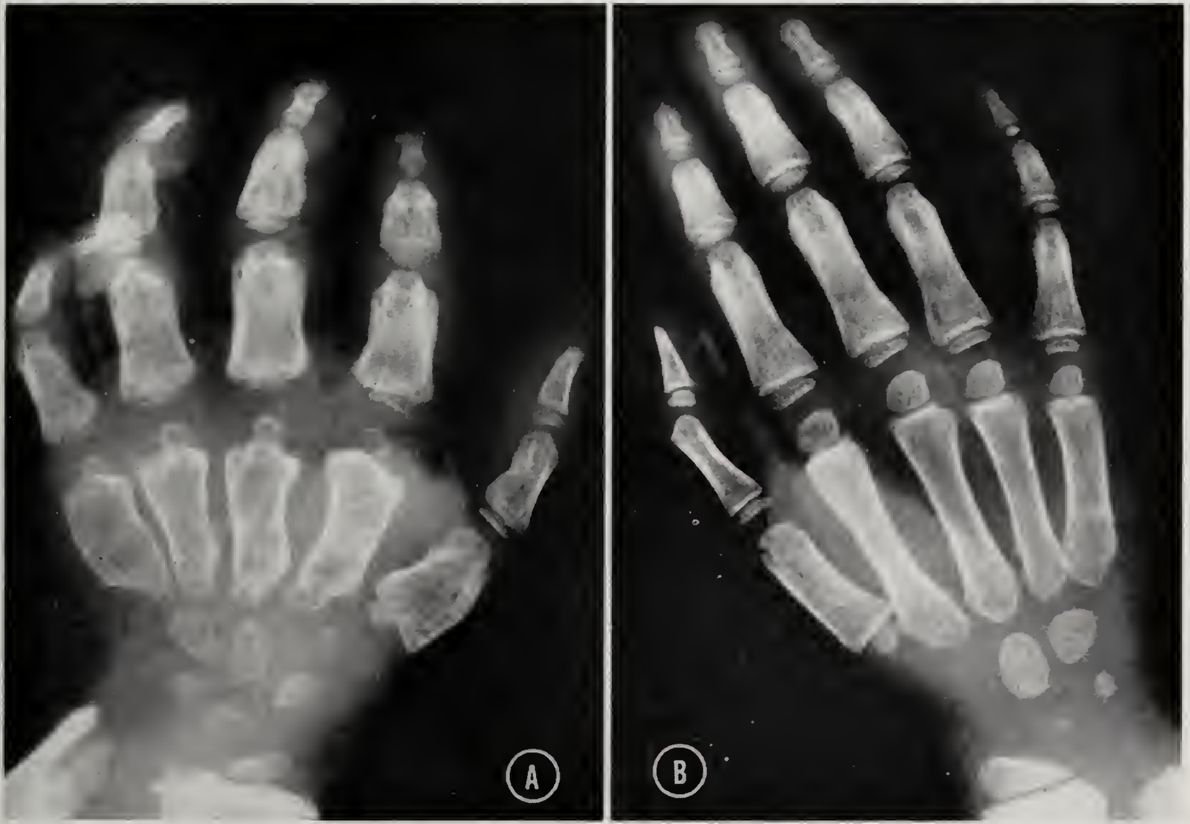

FIG. 3. A. Hand and wrist of a mixed excretor at age of 8 years; note pronounced bony abnormality. B. Hands and wrists of a 5-year-old girl who excretes heparitin sulfate predominantly. Except for slight retardation of bone age, osseous structures are normal.

by Bellon[19] and Zellweger et al.[20] Otherwise the problem in diagnosis is encountered only when there are very minimal or early osseous changes.

Abnormalities in Mucopolysaccharides and Amino Acids

Dr. Owen Rennert: The acid mucopolysaccharides are characterized by repeating disaccharide units of an amino sugar and a uronic acid linked by alternating 1—3, 1—4 B-glycoside bonds. In the normal state these substances are covalently linked to protein and are ubiquitous in their distribution. They play an important role in water and electrolyte metabolism, in calicification, in blood coagulation, in wound healing, and in other physiologic functions. Investigations over the past 3 years, predominantly by L. Roden and his associates,[21] have established that the chondroitin 4- and 6-sulfate glycoprotein bond occurs through a hydroxy linkage of serine.

To define the chemical defect which permits the accumulation of abnormal quantities of acid mucopolysaccharides in this disease, investigations in various laboratories have focused on the biosynthesis and catabolism of these polymers. At present there is no evidence to support the contention that a defect exists in the biosynthesis of mucopolysaccharides.[22] It is possible to explain the chemical findings in at least 2 additional ways: a deficiency in the degradative enzymes of the mucopolysaccharide-protein complexes and an anomaly in the complexing of the protein and mucopolysaccharides. An electron microscopic study of Van Hoof and Hers[23] indicates that in tissue from these patients the mucopolysaccharide is concentrated around lysosomal structures. This finding is compatible with an absence of lytic enzymes of the polysaccharide-protein complex.

One of the features which further characterizes these pathologic tissues is that aqueous extraction results in the isolation of acid mucopolysaccharide, whereas no AMPS is obtained when normal tissue is treated in such a manner. This implies that these mucopolysaccharides are not covalently linked to protein in the disease state. Utilizing aqueous extraction methods, Knecht and Dorfman[24] have demonstrated that HMS obtained from the spleens of these patients contains only a small proportion of the covalently linked amino acids normally found. In addition their data indicate that in Hunter-Hurler's AMPS, serine which links the AMPS and protein has a lowered serine per polysaccharide chain ratio than in AMPS obtained from normal tissue.

In an effort to demonstrate whether or not an abnormality existed in amino acid or protein metabolism in these patients their urinary and plasma amino acids were investigated. Table 2 presents in a condensed form the excretion of urinary amino acids in these patients and in normals. Eleven patients with this disease were investigated. Nine showed increased levels of urinary serine and tryptophane; the remaining 2 had levels at the upper limit of normal.

TABLE 2: Urinary Amino Acids in Hunter-Hurler Patients and in Normal Children Under the Age of Ten Years in mM./24 Hours

	Patients		Mean (11 Patients)	Normal Mean	Scriver[30] Range
	C.B.	M.G.			
Taurine	—	.060	.060	.081	.022–.185
Aspartic acid	.073	.051	.035	.041	.010–.220
Threonine	.475	.086	.128	.168	0.20–.300
Serine	.382	.227	.162	.037	.021–.062
Glutamic acid	.030	.046	.027	—	
Citrulline	.020	.018	.008	—	
Glycine	.637	.739	.329	.670	.160–1.42
Alanine	.222	.214	.130	.233	.012–.440
Valine	.060	.155	.042	.030	.015–0.50
Methionine	.024	.018	.016	.051	.020–.095
Cystine	.171	.093	.060	—	
β-Aminoiso-butyric	.119	.183	.064	.115	.045–.166
Isoleucine	.128	.267	.075	.034	.018–.056
Leucine	.237	.195	.094	.044	.027–.083
Tyrosine	.109	.044	.035	.084	.042–.169
Phenylalanine	.080	.046	.031	.046	.024–.106
Tryptophane	.371	.247	.258	—	
Gamma-amino-butyric	.109	.132	.064	—	
Ornithine	.069	.074	.030	—	
Lysine	.247	.342	.128	.290	.070–.640
Histidine	.247	.166	.128	.650	.306–1.28
Carmosine	.145	.163	.071	—	
Arginine	—	.008	.008	—	
Dopa	.053	.100	.074	—	
α-Amino N/24 Hrs.		33			

Examination of the plasma showed that all the patients had elevated levels of serine, but tryptophane and other amino acids in the plasma were within normal limits. Tryptophane-loading tests were performed on several patients, and all were within normal limits. No correlation could be made between the qualitative pattern of mucopolysaccharides excreted by these patients and the extent of their amino-aciduria. The patients studied were in varying degrees of debilitation from their illness, yet all but 1 showed this relatively specific amino-aciduria without a generalized amino-aciduria. We believe that the elevated levels of plasma and urinary serine are secondary to the derangement of mucopolysaccharide metabolism in this syndrome. Perhaps the abnormal levels of serine reflect the anomalous bonding between acid mucopolysaccharides and protein; in this connection serine may play an important role.

Modification of Excretion of Urinary AMPS

DR. ANATOLE DEKABAN: In a general way, the underlying disturbance of metabolism in Hunter-Hurler's syndrome would fall into one of 2 main categories: excessive production of AMPS, and deficient catabolism of AMPS.

In turn, each of these categories could be a result of diverse mechanisms. Thus, (1) excessively accumulated AMPS may have a different structure from those present in normal individuals, (2) there may be an enzymatic defect either in anabolic or catabolic processes, and (3) the linkage of AMPS to protein may be abnormal, or there still may be other possibilities.

In order to gain some information of a general trend in the deranged metabolism, we have attempted to modify the urinary excretion of AMPS in patients with the syndrome. Thyroid, corticosteroids, human growth hormone, chloroquine, and salicylates were used. Total 24-hour urinary AMPS were determined when the patients were in basic condition and while on medication. The AMPS were precipitated with cetyltrimethylammonium bromide[25, 26] and purified. The purified AMPS were separated into their constituents, largely chondroitin sulfate B and heparitin sulfate, by means of electrophoresis (Spinco Model H) in 0.1 M formic acid buffer of pH 4.8.

Results of these preliminary studies are given in tables 3, 4 and 5. For the purpose of comparison it was necessary to provide means and standard deviations of the 24-hour urinary excretion of AMPS when these patients were in basic condition and on a constant diet. According to Linker and Terry[27] and Berggard and Bearn[28] the excretion of AMPS by normal subjects varies between a few and 20 mg. per 24-hour urine. In table 3 the average daily excretion of AMPS in 6 patients is shown to range from 87 to 225 mg. Patients in the very advanced stage, who were completely confined to bed, tended to excrete greater amounts of AMPS than those who were still ambulatory, but this was not invariably so. The patients identified as M.K. and V.V. excreted predominantly heparitin sulfate (90–95 per cent), whereas the remaining 4 were mixed excretors. We have no clear evidence that any of these patients belonged to the sex-linked variant.

TABLE 3: Averages and Ranges of Total Urinary Mucopolysaccharides in Mg. per 24 Hours in Six Patients with Hunter-Hurler Syndrome, and Averages of Ratios of Chondroitin Sulfate B to Heparitin Sulfate (CSB/HS)

	M.H.	P.H.	T.E.	K.J.	M.K.	V.V.
AMPS Total	225±15	275±25	95±5	134±21	147±16	87
CSB/HS Ratio	40/60	58/42	49/51	20/80	0–10/90–100	0–10/90–100

Table 4 shows total urinary AMPS when the patients were established on various compounds.

TABLE 4: Total Mucopolysaccharide Excretion in Mg. per 24 Hours by Patients Receiving Various Compounds

	M.H.	P.H.	T.E.	K.J.	M.K.
Basic state	225±15	275±25	93±5	134±21	147±16
Thyroid			105	155	175
Corticosteroids	185		74		123
HGH*					170
Aralen			170	211	215
Salicylate		236			118

* Human growth hormone.

The 24-hour urines were collected between the fifth and seventh days of medication, and at least a 1-week interval in the basic condition separated the administration of another compound. The data are still incomplete, but there is a suggestive trend to indicate that while receiving glucosteroids the patients' total urinary excretion of AMPS diminished and while on chloroquine phosphate the daily excretion increased.

TABLE 5: Ratios of Chondroitin Sulfate B to Heparitin Sulfate in Urinary Mucopolysaccharides of Patients Receiving Various Compounds

	M.H.	P.H.	T.E.	K.J	M.K.
Basic state	40/60	58/42	49/51	20/80	0–10/90–100
Thyroid			44/56	11/88	38/62
Corticosteroids	25/75		34/66		35/65
HGH*					26/74
Aralen			46/54	27/73	12/88
Salicylate		50/50			12/88

* Human growth hormone.

Table 5 shows that the ratios of chondroitin sulfate B to heparitin sulfate can be modified (especially M.K., predominant excretor of heparin sulfate) by administration of thyroid, glucosteroids and growth hormone but not by Aralen® or salicylates.

The following tentative deductions can be made from these data: First, it is possible to increase or decrease the total urinary excretion of AMPS by administration of certain hormones or other compounds. Second, the ratio of chondroitin sulfate B to heparitin sulfate in the excreted AMPS can be altered. The relative ease in changing the ratio of chondroitin sulfate B to heparitin sulfate argues against using the ratio as a criterion for classification of variants of the disease.

A few patients were maintained for several weeks on some of these compounds and their clinical status assessed. The seemingly paradoxical finding of a slight clinical improvement, which paralleled both the increase and decrease of urinary excretion of AMPS, can possibly be explained. Corticosteroids may tend to decrease the production of AMPS,[29] while hydroxychloroquine appears to facilitate its excretion; thus, in both instances the amount of AMPS in tissues is likely to be reduced.

Summary

The Hunter-Hurler syndrome is an inborn error of mucopolysaccharide metabolism. The roentgenographic findings in this disease are characteristic and permit one to distinguish between mixed mucopolysaccharide and predominant heparitin sulfate excretors. The AMPS stored and excreted in Hunter-Hurler syndrome contain fewer amino acids bound to them and are probably linked in a different manner with the proteins. It has been shown that the patients with this disease have elevated levels of plasma and urinary serine. The role which this amino acid may play in mucopolysaccharide metabolism has been discussed. The total 24-hour urinary excretion of AMPS as well as the ratios of chondroitin sulfate B to heparitin sulfate can be altered by the administration of certain hormones and other compounds to the patients.

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Respiratory Failure Following Intramural Bowel Injection of Neomycin

Report of a Case

CAPTAIN RANDALL W. BELL, MC, USA*, AND COLONEL JOHN A. JENICEK, MC, USA†

THE REPORTS of Pridgen[1] and others during the 1950's focused attention on neomycin as a cause of respiratory apnea. Typically, within 20 to 30 minutes after intraperitoneal irrigation with dilute neomycin solution, a curare-like phenomenon occurred and the patient became apneic. Several fatalities were reported. This report describes an untoward surgical-anesthetic complication following neomycin injection into the bowel.

Report of Case

A 66-year-old retired sergeant presented symptoms of abdominal pain of 3 days' duration. A pulsatile abdominal mass had been noted 8 months previously during a hospitalization for acute myocardial infarction and was felt to be increasing in size on the day of this hospital admission. The patient was anorexic and had low back pain attributed to known spondylolisthesis. He had been constipated for 3 days. The history included diverticulosis of the colon, appendectomy at the age of 17, right-sided cerebrovascular accident at the age of 63, intermittent claudication, and chronic renal disease.

The patient was in acute distress with right lower quadrant abdominal pain. There was a 12 cm. pulsatile midline abdominal mass with bilateral femoral bruits, anterior rectal wall tenderness, and decreased right leg pulses. The white blood cell count was 10,500 with a normal differential count. Urinalysis, serum Na, Cl, K, and CO_2 were normal, but the blood urea nitrogen was 68 mg. An electrocardiogram showed marked left ventricular hypertrophy and possible electrolyte imbalance. Chest and abdominal roentgenograms were noncontributory. Excretory urograms revealed delayed bilateral function at 10 minutes.

At laparotomy the abdominal aortic aneurysm was intact; however, a recent 1 cm. perforating diverticulitis was found. Prior to sleeve resection about 70 c.c. of 1 per cent neomycin solution was injected into the lumen of the bowel. By accident 10 c.c. spilled into the peritoneal cavity and another 10 to 15 c.c. was deposited within the wall of the bowel.

General anesthesia had been induced with thiopental, followed by nitrous oxide, ether and oxygen. Endotracheal intubation was accomplished 10 minutes after induction with a single dose (60 mg.) of succinylcholine chloride. Six mg. of d-tubocurarine chloride was given during the first hour of anesthesia. A gas-oxygen-ether mixture was administered with assisted respirations, except for a 45-minute period of controlled ventilation by a mechanical ventilator. The total anesthesia time was 3 hours and 20 minutes. Vital signs throughout showed no abnormalities and no significant deviations. A 500 c.c. estimated blood loss was recorded. Fluid replacement consisted of 1,800 ml. of Ringer's lactate solution and 400 c.c. of 5 per cent dextrose solution. The anesthetist noted that spontaneous respirations were slow in returning but seemed adequate when the patient arrived on the recovery ward.

The patient received lincomycin, chloramphenicol, and streptomycin postoperatively. Three hours after the neomycin injection he developed sudden respiratory paralysis, cyanosis, vascular collapse, and loss of arterial pulsations. Mouth-to-mouth ventilation followed immediately by endotracheal intubation and closed chest cardiac compression was begun within 60 seconds. Myocardial activity and normal blood pressure promptly returned. An electrocardiogram showed no change from previous tracings. The patient was placed on controlled and then assisted artificial ventilation for 12 hours and made an uneventful recovery.

Discussion

Neomycin irrigation of the bowel or peritoneal cavity before or during gastrointestinal surgery is done to reduce saprophytic and possibly pathogenic organisms. The original pharmacologic studies on neomycin by Waksman[2] revealed a mouse toxic dose of 125 mg./Kg. with death by apnea. It was not until after a growing awareness of apneic deaths following peritoneal instillation of neomycin that this toxicity

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was explored. Pittinger[3] showed a potentiating effect of both neomycin and streptomycin on d-tubocurarine chloride and succinylcholine chloride. In dogs a 65 per cent effective nondepolarizing type of neuromuscular blockade developed with 25 mg./Kg. of neomycin alone. With 75 mg./Kg. of d-tubocurarine only 15 mg./Kg. of neomycin caused 97 per cent paralysis of neuromuscular action or a 2,000-fold difference. Sabawala et al[4] implicated polymyxin as another apneic-producing antibiotic and thought that ether potentiated this toxicity. Cyclopropane, because of its inotropic action, was regarded as the anesthetic of choice when neomycin was administered. Studies on human respiratory muscle showed a peak toxic effect of neomycin at 150 minutes. Typical reported cases involved the intraperitoneal instillation of 50 to 200 c.c. of 1 per cent neomycin solution. Ether was the usual anesthetic, and the patients were often atropinized, implicating the anticholinergic agents. Apnea occurred within 20 to 30 minutes after the injection, causing an initially high fatality rate of over 50 per cent.[1]

In such cases of neomycin-related apnea neostigmine was administered with good effect, reversing the curare-like phenomenon through its anticholinesterase action.[5] However, neostigmine also enhances gastric contractions, increases gastric secretions, and stimulates tone and peristalsis in the lower esophagus, small bowel, and particularly the colon.[6] It is therefore contraindicated in a patient immediately after colonic resection.

Apnea occurred about 3 hours after administration of the antibiotic, which is later than the acute onset previously reported in the literature but for higher amounts of intraperitoneal solution. This time corresponds to the experimental peak toxic effect of 150 minutes. The small intramural dose of neomycin and the postoperative use of intramuscular streptomycin in 1 or 2 hours would also delay this peak effect.

Summary

In a patient thought to have a rupturing abdominal aortic aneurysm, acute perforating diverticulitis was discovered at laparotomy. As a bowel preparation, 1 per cent neomycin solution was instilled intraluminally with some peritoneal spillage and with some intramural injection of the antibiotic. Respiratory arrest occurred 3 hours after the injection and was specifically treated by artificial ventilation until the drug was biotransformed. The peculiar curariform toxicity of neomycin and to a lesser extent streptomycin has been emphasized. The anesthesiologist and surgeon should be prepared to support ventilation in the immediate postoperative period if such a patient is to survive.

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The Complete Gastrointestinal Study: A Wise Investment

CHARLES E. BICKHAM, JR., M.D.*

In a recent review of 1,700 upper gastrointestinal studies it was noted that there were 756 patients in whom the upper gastrointestinal tract and the colon were examined simultaneously. This group of 756 patients were further studied and appraised to determine whether such complete X-ray studies revealed enough valuable information to be ordered routinely when patients present themselves with noncomplicating symptoms referable to the digestive tract.

Indications for X-ray Examination of the Gastrointestinal Tract

The roentgen examination of the gastrointestinal tract is the most valuable aid available in the study of digestive disorders. The indications for this procedure are the following:

1. Any patient complaining of digestive symptoms, however vague, should have a thorough X-ray examination of the gastrointestinal tract, even though the diagnosis is strongly suspected by the history, physical examination, and other laboratory tests. The radiologic examination provides an intelligent approach to the confirmation or exclusion of the diagnosis and to the therapeutic management of the patient. At the same time the procedure reduces the margin of error which might produce serious complications and undue economic hardships.
2. The roentgen examination should be employed to differentiate between organic disease and functional disorders.
3. Hemorrhage from the digestive tract should always be investigated by radiologic methods unless the patient's condition is such that it would seriously endanger his life.
4. Suspected obstruction in both upper and lower tracts may be safely investigated with close supervision of the patient.
5. The examination may lead to the diagnosis of unsuspected lesions not only in the gastrointestinal tract but also in the biliary, genitourinary, cardiovascular, pulmonary, hematologic, and skeletal systems. Silent lesions may be detected which could exist for long periods of time and which could grow and eventually prove fatal.
6. The investigation is a valuable adjunct in giving the physician an idea of the patient's general condition.

Techniques of Investigation

Modern radiologic practice in the detection of diseases affecting the digestive tract demands the employment of certain time-tested and approved methods whose worth has been amply demonstrated. The techniques usually consist of the following:

1. Posterior-anterior chest survey film
2. Abdominal scout film
3. Upper gastrointestinal examination
4. Colon examination
5. Cholecystographic examination.

The patient should be examined both fluoroscopically and by means of film to make a permanent record. The development of television fluoroscopic equipment in recent years has been one of the major advancements in radiology. Its use has contributed considerably to accuracy in diagnosis, reduction of radiation to the patient, and excellent patient coöperation, since the procedure is carried out in an illuminated room.

Cholecystography should be done routinely as a part of the complete gastrointestinal study. In upper abdominal disturbances biliary disease and peptic ulcer often cannot be differentiated clinically.

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Dangers of the Radiologic Examinations

The use of the roentgen examination should be done by one not only skilled in fluoroscopy and interpretation of film but also by one who has a knowledge and respect for the lethal effects that X-rays have on living cells. The haphazard and inexperienced use of the fluoroscope may lead to damage physically to the operator and patient as well. Erroneous diagnoses may lead to dangers far greater than those produced by direct tissue damage from the roentgen rays themselves. With this knowledge, this form of energy can be used safely.

Results in 756 Patients

The 756 patients were private hospital and outpatients ranging in age from 3 months to 91 years. There were no pathologic findings in 155 or 20.5 per cent, but in the other 601 patients there were 975 organic abnormalities either in the gastrointestinal tract, chest, abdomen, or skeleton. In assessing the results of this study one must be reminded that in many instances the symptoms and physical findings were such that both examinations were indicated or else a complete study was desired for other reasons. The finding of acute conditions in this group was low, because when symptoms are specifically referable to a specific system the study would have been directed only to that tract.

Table 1 lists the most important abnormalities found in the upper gastrointestinal system. Hiatal hernia was the most common lesion. Duodenal ulcer and deformed duodenal bulbs due to ulcer, as might be expected, were next in frequency. Benign gastric ulcer was 4 times as common as carcinoma of the stomach.

TABLE 1: Upper Gastrointestinal Abnormalities

Hiatal hernia	230
Duodenal ulcer	42
Deformed duodenal bulbs from ulcer	33
Duodenal diverticula	33
Benign gastric ulcer	27
Gastroduodenitis	24
Gastric resections for peptic ulcer	17
Esophageal diverticula	14
Carcinoma of the stomach	7
Regional ileitis	5
Zenker's pulsion diverticula	4
Esophageal varices	4
Polypoid lesions of the duodenum	3
Benign tumors of the stomach	2
Cardiospasm	2
Pancreatic carcinoma	2
Intrathoracic stomach	1
TOTAL	450

The colon examination results are tabulated in table 2. Diverticula are very common in the colon, and the incidence of complications is low in this series, apparently because in the symptomatic patient usually only the barium enema would be specifically ordered. The same reasoning is true concerning both the benign and malignant tumors of the colon, which usually present more dramatic symptoms, such as hemorrhage, obstruction, anemia, etc. Redundancy was present in 63 patients, and it may be significant as one of the causes of constipation, and it may also result in volvulus.

TABLE 2: Colon Abnormalities

Colon diverticula	284
Redundant colon	63
Polyps (patients)	29
Carcinoma of the colon	14
Malrotation of the colon	9
Diverticulitis and abscess formation	8
Ulcerative colitis	6
Right colectomies	5
Metastatic carcinoma to the colon	2
Endometriosis	1
Megacolon	1
TOTAL	422

The chest survey studies (table 3) produced only a very small amount of pathologic findings. The possible routine use of this examination might be omitted because of such a low return.

TABLE 3: Chest Lesions

Left ventricular enlargement	23
Emphysema	4
Aortic valve calcification	2
Carcinoma of the lung	1
Metastatic carcinoma of the lung	1
TOTAL	31

The abdominal scout films (table 4) provided unusually significant abnormalities. The abdominal survey film is extremely important and should always be done prior to the gastrointestinal study, since it may provide the clue leading to the prompt and accurate diagnosis of abdominal diseases. Biliary disease and peptic ulcer are almost impossible to differentiate clinically at times. Cholecystograms were done and confirmed the presence of gallstones in 15 patients and cholesterol polyps in 2 others. There were 4 cases in which the calcifications were typical of gallstones on the scout films, but cholecystograms were not done to confirm their location. Other important findings noted on the abdominal films were pelvic and abdominal masses, suspected renal stones, and aortic aneurysms.

TABLE 4: Abdominal Lesions

Suspected abdominal and pelvic masses	17
Gallstones proven by cholecystography	15
Suspected renal stones	12
Aortic aneurysms	5
Suspected gallstones (no cholecystograms)	4
Ascites	4
Inguinal hernia	4
Fecal impaction	2
Metastatic carcinoma of the spine	2
Cholesterol polyps in the gallbladder	2
Pancreatic calcifications	2
Distended urinary bladder	1
Calcified adrenal gland	1
Hydronephrosis	1
TOTAL	72

Conclusions

The proved worth of the complete roentgenologic examination amply justifies its wide utilization in the study of any patient with digestive symptoms without serious complications. In complicated cases the investigation may be limited to a particular area or system.

The studies reveal important pathologic findings not only in the gastrointestinal tract but in other systems as well.

Unsuspected silent lesions may be discovered which may prove life-saving.

X-ray television systems have improved the accuracy in diagnosis and at the same time have reduced the hazards of radiation exposure to patient and operator.

Organic disorders are separated from functional disorders.

The complete roentgen examination of the digestive tract is rewarding and is a most wise investment in patient care and management. The value received is well worth the effort expended.

Ten Commandments for Illustrating Lectures

SPEAKING BEFORE A GROUP of about 100 officers and civilians assembled at the Walter Reed Army Institute of Research in December 1965, Colonel Robert Ollerenshaw, prominent British medical illustrator, presented what some listeners called "Ollerenshaw's 10 Commandments for Illustrating Lectures."

The speaker, who holds many titles and honors in his field, is Director of the Department of Medical Illustration for the Royal Infirmary in Manchester, England. He is also Honorary Surgeon to Her Majesty the Queen.

Speaking of the many pitfalls encountered in the illustrated lecture, Dr. Ollerenshaw said: "We can't measure personal tastes in design, nor can we define an average audience." But as a guide to those called upon to give lectures, he gave the following suggestions:

1. Selection of typefaces is important. They should be of medium density; large block letters and fancy frills are out.

2. Design is important. Esthetics makes a big difference in obtaining a favorable audience reaction.

3. The lecturer should aim simultaneously toward the 2 most powerful senses, sight and sound.

4. Diagrams and charts should have a minimum of labeling, leaving it to the lecturer to explain the contents of the slides.

5. Overhead projectors are not as practical as standard slide projectors. Most lecturers are poor printers, and an overhead projector magnifies errors and imperfections, thereby distracting the audience.

6. Slides should not be crowded. In newspaper parlance, a picture is worth a thousand words. But the picture itself should not attempt to contain the thousand words.

7. Proper use of color can be "eye-catchers." Reds and yellows—the advancing colors of the artist—are best for varying degrees of light and distance.

8. Illustrations used by the lecturer should be easily understood by both professionals and laymen.

9. The lecturer and the projectionist should coördinate their efforts. The speaker must always know that the right slide is being presented at the right time.

10. Always check visibility features in the lecture hall. Size of the screen is very important to the audience in the front rows as well as to those in the back of the room. Example: A small screen should not be used for a large audience, or vice versa.

PRESIDENT'S PAGE

FOR CHANGING TRENDS, A STRONG SOCIETY

During my tenure as President of the Medical Society of the District of Columbia I have had an opportunity to acquaint myself with many state medical organizations throughout the country. These experiences have permitted certain comparisons which have left me with a real sense of pride in our Society.

One has only to read the history of our organization to realize that its growth from a handful of physicians to a membership of 2,443 could only result from the efforts and interests of a long series of earnest and farsighted members. At present all elements of our medical community participate in an intimate fashion in the affairs of the Medical Society of the District of Columbia.

Our new Headquarters has done much to enhance the communal spirit. So often visitors express amazement that in a metropolitan area having 3 schools of medicine, the academic and the clinical interests are so effectively merged.

With growth, operational problems become compounded and administration becomes more and more demanding. It is a tribute to our Society's staff, led by a wise and prudent Executive Director, that the activities of the Society are conducted with a degree of dispatch and efficiency that I have not observed elsewhere.

With the changing trends that are taking place in medicine, we are fortunate in being heirs of a strong organization that can represent leadership and a "united front" to the District of Columbia and its environs.

Robert J. Coffey.

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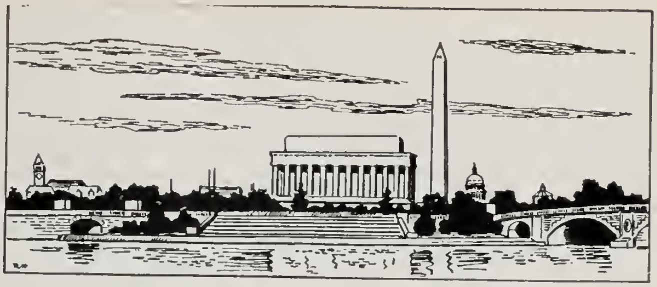

EDITORIALS

Disaster Training Seminar and Drill

On September 29 and 30 and on October 1, 1966, a Metropolitan Area Professions Disaster Training Seminar was conducted in Washington, D. C., with representatives present from the D. C. Medical Society, Montgomery County (Md.) Medical Society, Alexandria City (Va.) Medical Society, D. C. Chapter of the American Red Cross, Hospital Council of the National Capital Area, D. C. Pharmaceutical Association, D. C. Nurses' Association, D. C. Dental Society, Veterinary Medical Association of D. C., the D. C. Police and Fire Departments and the Departments of Public Health and Public Welfare, and the Maryland State Department of Health.

The Seminar was developed as part of a continuing program to encourage and to assist the various allied health personnel in achieving greater proficiency in medical preparedness for natural and man-made disasters and to stimulate interest in the establishment of mutual support and recognition in the District of Columbia and in nearby counties.

The first 2 days of the Seminar consisted of lectures and panel discussions on the responsibilities of all health disciplines during disaster. The third day was devoted to a Metropolitan Area Hospital Disaster Drill, triage, and the use of the packaged-disaster hospital at the D. C. Armory. Ten hospitals and approximately 600 "patients" participated in this exercise.

A critique was held at the D. C. Medical Society auditorium after the drill had been completed, and the umpires (doctors) reported on the performance of each hospital during the drill. The final decision was that there is a need for this type of seminar and drill to be held annually.

A vast number of unique and complex problems were encountered in the planning for and the presentation of the 3-day program. Our experience will be of benefit in future requirements.

Drs. John W. Latimer, Jr., and W. Ronald Strong, Chairman and Vice Chairman, respectively, of the Committee on Emergency Medical Service, D. C. Medical Society, and Dr. Charles J. Savarese, Jr., of the Montgomery County Medical Society, were among the speakers at the Seminar. These 3 doctors worked closely with the Division of Health Mobilization, D. C. Department of Public Health, in coördinating the activities of the Seminar and the Disaster Drill.

H. S. Meek
Chief, Division of Health
Mobilization, District of
Columbia Health Department

Too Many Babies—Not Enough Adoptive Parents

Placement of a baby in adoption is no longer a simple matter. An expectant mother making her first phone call to an agency is likely to be deluged with questions: her age, marital status, date of delivery, state of residence, religion, and the whereabouts of the father of the child. The questions may seem irrelevant to her and not particularly sympathetic of her plight. It is necessary for any agency worker to ask these questions in order to locate the one agency which will accept her in an oversubscribed field of social services.

The requests for adoptive placement by the ex-

Opinions expressed in contributions to the Editorial Section are those of the writers and do not necessarily reflect the views of the Medical Society of the District of Columbia

pectant mother have increased steadily in the last 5 years. The agencies are unable to keep up with the demand. For reasons of agency policy, or dearth of social workers and boarding homes for babies, most private agencies have restricted their "intake" to the number of unmarried mothers they feel they can handle properly.

The public welfare agencies may turn away nonresident girls, but they assume full responsibility for the unmarried mothers who have a 1-year residency in their locale. Add to this the various denominational agencies who give preferential help to those of their own faith, and the confusion is compounded.

For example, it is most unlikely that in the District of Columbia a nonresident girl without religious affiliation, unwilling to contact the baby's father, whose delivery date is imminent, will be accepted for adoption of her child. If she is a Negro, her chances are even more remote. She will be advised to return to her home state and to avail herself of public welfare assistance there. When she left home, to hide her pregnancy and to seek medical care in a distant city, she did not anticipate any difficulty with the adoption. Like many people, she assumed that adoptive parents are plentiful and the process of adoption simple.

Neither of these assumptions is correct. The number of adoptive parents has not kept pace with the babies available for adoption. The changes in the ratio of adoptive parents to children have been so rapid that agency workers are breathless from adapting to the new situation. Whereas restrictions of an arbitrary nature used to be imposed on the adoptive parents when the ratio was 10 to 1, the agencies are now aggressively seeking adoptive parents and guiltily turning away unmarried mothers they might once have been eager to help.

The Adoption Service of the Washington Home for Foundlings has its restrictions too. Our Agency policy requires that the unmarried mother allow the Agency to contact the father of the child for background history, medical information, and his consent to adoption. We justify this policy, which as a selective process eliminates many girls in need, by asking no other requirements of her. An expectant mother and father of any color, race or creed, or place of residence, is served by us. She may come to us early or late in her pregnancy, or even after the baby is born.

Functioning in this way, we serve our community well. We handle 100 babies yearly and make 80 adoptive placements. No longer do we find many mothers who refuse to contact the fathers of their babies.

The numbers of adoptions we make are limited now, not by the restriction imposed in our policy of father participation but by the numbers of adoptive parents available.

Our standards of placement remain the same: the placement of a baby into adoptive homes appropriate to each child, with special concern for the similarities between the 2 sets of parents and the character of the emerging small individual with whose full and good life we are concerned.

Linda C. Burgess
Executive Director, Peirce-Warwick Adoption Service, Washington Home for Foundlings

Friendly Dog Syndrome*

Large numbers of people are bitten by "friendly dogs," many more than is commonly believed. The figures when searched for are astounding and shocking.

The injury is sustained when least expected, so much so that a clear picture of just what happened is usually not obtained. This is especially true with children.

Man has not learned how to live with dogs. He treats the dog as a completely domesticated animal when in reality he is part wild. We respect wild horses until we've trained them. Even so, we don't take chances lest the animal bite or kick. We assume too much in our relationships with dogs and foolishly abandon fundamental rules. I am not condemning dogs, any more than I would the automobiles which killed 47,000 people last year in this country alone. The pet population of this country is in the category of big business. The cat- and dog-food industry does a volume estimated at $550 million yearly, and Americans spend more than $3 billion yearly on a pet population of 54 million cats and dogs, 20 million parakeets and canaries, and 1 million assorted snakes, hamsters, monkeys, and other friends of man. A few rules of behavior may prevent a number of dog bites:

1. Above all, do not hold your face close to a dog.

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* Reprinted in part and by permission from New York J. Med., 1966 **66**, 2306 (September 1).

2. Do not permit your dog to roam at large. Keep him on a leash under your control. The city of Dallas reported a 50 per cent drop in reported dog bites following the passage of a city leash law.

3. Do not permit a young person to lead a large dog.

4. Do not pet a strange dog. Not knowing and misinterpreting your intention, the animal may reward you with a bite.

5. Do not tease a dog, pull its tail, or take away food, a bone, or a toy with which he is playing.

6. Do not run in front of a dog while on skates or a bicycle. It startles him and he may bite.

7. Do not touch a dog while he is asleep or is unaware of you.

8. Do not permit your dog to stray.

9. Vaccinate your dog periodically against rabies for the safety of your dog and your family.

10. Keep your dog on a leash or confined to a safe area when accepting deliveries of mail or packages from delivery boys.

11. Do not give a dog to children under at least 6 years of age. Teach them how to take care of their pets and not to abuse them. A dog will take only so much even from the immediate family.

12. A dog owner has the responsibility of training his animal. Any dog can become a "bum," soiling your neighbor's sidewalks and howling during the night or when left alone. "Man's best friend" can also become a pest. Proper training, discipline, and care are essential. Training a dog requires effort and some cost. If you are not willing to invest in this, don't have a dog. A dog can turn into an outlaw and become vicious and should then be destroyed or sent somewhere where he can be taken care of properly. It has been difficult to determine if there is any special breed of dog that would be less likely to bite people. There is no safe breed. Any dog without proper training and under provoking circumstances will turn and bite even members of the immediate family on their own premises.

13. Again, above all, do not hold your face close to a dog.

The local lesions, no matter how extensive, are treated as any other lacerations. Copious washing with soap and water and irrigation with a benzalkonium chloride solution is followed by primary closure with accepted surgical techniques. These wounds heal well. Rabies treatment will depend on the examination of the animal.

The old adage that every dog is entitled to 1 free bite is passing into oblivion. Many states have passed strict liability laws leaving little room for argument as to who did what to whom, how provoked the dog was, and so on. If he bites, you pay. This is particularly true where children are involved, and the majority of bites involve children. The dog may be implicated indirectly in liability when he may cause an accident by frightening a child on a bike or skates or even a passing motorist. Thus the dog owner has the necessity of providing himself with adequate liability insurance. One example will suffice: On October 20, 1964, a jury in White Plains, New York, awarded a $100,000 verdict to a plaintiff as a result of dog bites.

Daniel Klein, M.D.

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1 Hanson Place
Brooklyn, New York 11217

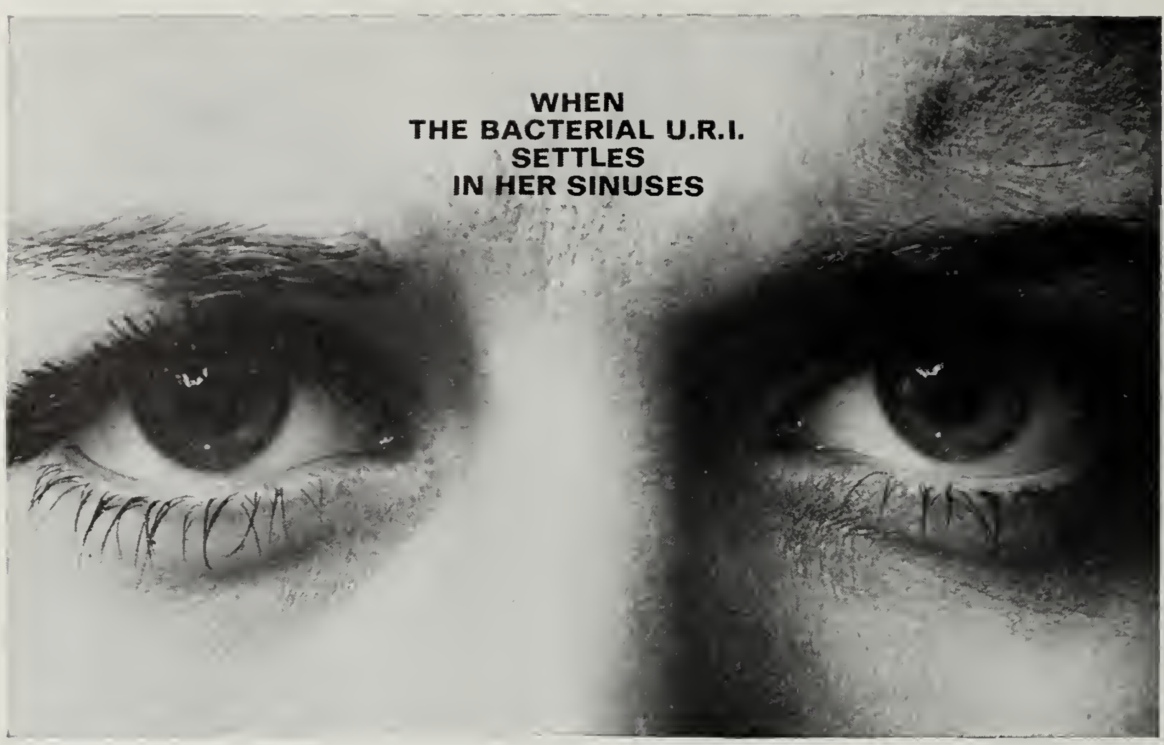
Obstetrical Care at the Washington Hospital Center

There are 2 types of facilities for obstetrical patients at the Washington Hospital Center, Family-centered Nursing Care in the rooming-in unit and Conventional Care on a maternity unit.

Classes called "Preparation for Parenthood" are offered for the expectant mother and father. They are held, twice a week for 3 weeks, with a new class at the beginning of each month, from 7:30 to 9:30 p.m. in order for the expectant parents to attend together.

Following is an outline of the material presented:

1. Anatomy and physiology of pregnancy
    a. Anatomy of the male and female reproductive system
    b. Characteristics of pregnancy
2. Nutrition and exercise
    a. Basic diet plan for weight control during pregnancy, 1,550 calories, providing essential nutrients as recommended by the National Research Council; salt free diets.
    b. Demonstration of exercises, breathing and relaxation from the book, "Psychophysical Preparation for Childbearing" by the Maternity Center Association of New York City.
3. Labor and delivery
    a. Anesthesia and particularly its value to the patient when indications favor its use.
    b. Establishment of a healthy perspective on child birth in order to accept either normal labor or obstetrical intervention, should that



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The patient can feel better while getting better. ACHROCIDIN brings the treatment together in a single prescription—prompt symptomatic relief together with early, potent control of the tetracycline-sensitive organisms frequently responsible for complications leading to prolonged disability in the susceptible patient.

Effective in controlling complicating tetracycline-sensitive bacterial infection and providing symptomatic relief in allergic diseases of the upper respiratory tract.

Contraindication—History of hypersensitivity to tetracycline.

Warning—If renal impairment exists, even usual doses may lead to liver toxicity. Under such conditions, lower than usual doses are indicated and if therapy is prolonged, tetracycline serum level determination may be advisable. Hypersensitive individuals may develop a photodynamic reaction to natural or artificial sunlight during use. Individuals with a history of photosensitivity reactions should avoid direct exposure while under treatment and treatment should be discontinued at first evidence of skin discomfort.

Precautions—Some individuals may experience drowsiness, anorexia, and slight gastric distress. If excessive drowsiness occurs, it may be necessary to increase the interval between doses. Persons on full dosage should not operate any vehicle. Use may result in overgrowth of nonsusceptible organisms. If infections appear during therapy, appropriate measures should be taken. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Infections caused by beta-hemolytic streptococci should be treated for at least 10 full days to help prevent rheumatic fever or acute glomerulonephritis. Use of tetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect has been observed in usual short treatment courses.

Average adult dosage: 2 tablets four times daily, given at least one hour before, or two hours after meals.

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necessity arise, with unswerving confidence in the technical skills and judgment of her obstetrician.
   c. Drugs that may be used to relax and to take the edge off the tension of the patient.
4. Requirements of the newborn
   A basic layette is demonstrated with a newborn baby from the Family-centered Nursing Care unit.
5. Economics and tour of the Department
   a. Cost of rooms and insurance coverage
   b. With covergowns on each person, a tour of the 2 units, Family-centered Nursing Care and Conventional Care; complete tour of admitting room, labor rooms and delivery rooms.
6. Movies
   a. Prenatal trimester progress
   b. "From Generation to Generation" in color: implantation and fertilization of cell
   c. "Management of Breast Feeding"
   d. "A Normal Birth"

By the third week and the fifth class the patients and their husbands are drawn together as a mutually interested group. They are now more able to communicate their feelings to the instructor and to each other.

After 7 years of conducting these classes we still do not pretend to be able to answer all the questions relating to modern-day obstetrics. There does not seem to be a significant change in the length and character of labor for persons who have attended these classes and persons who have not, but the evidence is strong that we are achieving the important objective of humanizing medical care and creating an atmosphere of friendliness in a maternity department of a modern hospital.

Ruth R. Goodman, R.N.
Instructor
C. K. Fraser, M.D.
Administrative Chairman
Departments of Obstetrics and Gynecology, Washington Hospital Center.

The Treatment of Salmonellosis (except S. Typhosa)

A Policy Statement of the D. C. Department of Public Health

Salmonella gastroenteritis in otherwise healthy persons is usually self-limited and the patients recover quickly. Such patients, as a rule, derive no benefit from antimicrobial therapy. On the other hand, infants, particularly premature ones, and young children and elderly persons may become severely ill and these types of patients may require treatment.

At present, active cases of salmonellosis or carriers are either advised to consult a private physician or are referred to D. C. General Hospital for treatment. While it is difficult to explain the rationale of withholding specific treatment from persons excluded from employment in certain categories (food handlers, nurses, those caring for children and the aged), present thinking indicates that recovery occurs more quickly in such persons than in those who are being treated. For example, in a recent local food-borne incident due to Salmonella, one food-handler receiving the most prolonged treatment continued to excrete organisms far beyond the period required by others involved in the same outbreak to recover. Various antibiotics were employed because of failure of those prescribed previously.

In a recent study among children infected with *S. typhimurium*, those receiving no treatment recovered in 15 weeks as compared to 18 weeks in the treated group. There is experimental evidence that antibiotic therapy may interfere with the normal flora of the intestinal tract and thus prolong the excretion of foreign organisms.[1]

According to Cecil-Loeb[2] there is no concrete evidence that antibiotics reduce either the duration of illness or the period of excretion of salmonellae in the stool. This is applicable to carriers as well as acute cases.

In Harrison's "Principles of Internal Medicine"[3] the effectiveness of antibiotics in acute and carrier stages is stated to be variable and unpredictable, usually ineffective in the latter.

It is suggested, therefore, that antibiotic treatment not be given to otherwise healthy patients with uncomplicated salmonella gastroenteritis.

Murray Grant, M.D., D.P.H.
D. C. Director of Public Health

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[1] Communicable Disease Center Salmonella Report No. 45, January 31, 1966; reprinted from Dixon, J. M. S.: Brit. Med. J., 1965, 2, 1343.

[2] Beeson, P. B., and McDermott, W., edited by: Cecil-Loeb Textbook of Medicine, 11th ed. Philadelphia: Saunders, 1963, p. 242.

[3] Harrison, T. R., and others, editors: Principles of Internal Medicine, 4th ed. New York: McGraw-Hill (Blakiston Div.), 1962, p. 948.

Night Leg Cramps...

Frequent Bedfellow in Diabetes, Arthritis, and Peripheral Vascular Disorders*

*"Nocturnal cramps occurring in the calf muscles and small muscles of the feet have been encountered in a significant number of diabetic patients."[1]

". . . nocturnal cramps may be the presenting symptoms of patients with arteriosclerosis obliterans, deep thrombophlebitis, varicose veins, osteoarthritis . . ."[2]

now... specific therapy for night leg cramps

QUINAMM™

Consistently effective, QUINAMM provided complete relief in 94% of 200 patients studied, many of whom were severe cases refractory to other medication.[3] Your prescription for one tablet at bedtime often controls painful night cramps with the initial dose . . . helps restore restful sleep.

QUINAMM Composition: Each white, beveled, compressed tablet contains: Quinine Sulfate 4 grains (250 mg.), Aminophylline 3 grains (200 mg.). **Precautions:** Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. **Contraindication:** QUINAMM is contraindicated in pregnancy because of its quinine content. **Dosage:** One tablet upon retiring. Where necessary, dosage may be increased to one tablet following the evening meal and one tablet upon retiring. **Supplied:** Bottles of 100 and 500 tablets. **Caution:** Federal law prohibits dispensing without prescription. **References:** 1. Shuman, C.: Am. J. Med. Sci., 225:54, 1953. 2. Perchuck, E., et al.: Angiology, 12:102, 1961. 3. Rawls, W. B., et al.: Med. Times, 87:818, 1959.

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The Role of the Medical Society in Disaster*

JOHN W. LATIMER, JR., M.D.

Chairman, Committee on Emergency Medical Service, The Medical Society of the District of Columbia

The most important role of a local Medical Society in disaster is to be prepared for it. The Medical Society of the District of Columbia has delegated this responsibility to its Committee on Emergency Medical Service. The prime objective of this Committee is to see that disaster casualties receive the best possible medical care at the earliest possible moment. This can be accomplished by using the following precepts as guidelines:

1. Develop definitive plans in coöperation with all other agencies and organizations which have responsibilities in disaster.
2. Implement, at the local level, the policies of the Committee on Disaster Medical Care of the American Medical Association.
3. Supply qualified physicians to direct first aid and triage at the disaster site and to aid health officers in the care of the sick and injured of the community in the wake of a disaster.
4. Attend conferences and symposia on disaster problems such as those sponsored by the AMA Committee on Disaster Medical Care.
5. Stimulate the interest of community nurses, dentists, medical technicians, veterinarians, pharmacists, and undertakers by defining their roles in disaster.
6. Test disaster programs of local hospitals by supervising hospital drills upon request, and in the community cosponsor community-wide disaster drills.
7. Establish classes to train medical and paramedical personnel in the technique of caring for mass casualties and assist and encourage community participation in the Medical Self-Help Program.
8. Represent the Medical Society and coöperate with government and nongovernment agencies and associations in matters involving medical and health problems during emergencies and disasters.

I shall elaborate on 2 of these precepts.

The first of the D-I-S-A-S-T-E-R precepts of the Medical Society which I should like to discuss is the D—Develop definitive plans in coöperation with other agencies and organizations which have responsibilities in disaster.

Efficient disaster care depends upon the coöperation and cohesiveness of all organizations concerned with disaster. The disaster committee of the Medical Society must be familiar with the functions and plans of these organizations and see that they are familiar with those of the Medical Society.

This function was greatly facilitated in the District of Columbia this year when Mr. Walter N. Tobriner, Chairman of the Board of Commissioners of the District of Columbia, appointed a committee to coördinate the efforts of all District of Columbia agencies and organizations having responsibilities during a time of disaster. The committee was ably chaired by Mr. Francis H. Cobb, Manager of the D. C. Chapter of the American Red Cross, and was composed of representatives of the Police and Fire Departments, the D. C. Health Department, the D. C. Office of Civil Defense, the D. C. Welfare Department, the D. C. Chapter of the American Red Cross, the Hospital Council of the National Capital Area, and the Medical Society of D. C. The work of this committee has resulted in the first documented disaster plan for the District of Columbia. It was completed in June 1966 and presented to Commissioner Tobriner, who has proclaimed it the official Natural Disaster Plan for the District of Columbia.

I should like to summarize the pertinent aspects of this report.

A. *Definition.* The plan is concerned with a natural disaster in distinction to one resulting from enemy attack. A natural disaster is defined as a flood, earthquake, tornado, hurricane, fire, explosion or wreck in which numbers of persons are plunged into helplessness and suffering.

B. *Command.* The ranking member of the Board of Commissioners available will assume command.

C. *Execution.* Each agency will be responsible for its internal operation and exert operational control of its own services but coördinate with each other as dictated by the Plan.

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* Read before the first Metropolitan Area Professions Disaster Training Seminar in Washington, D. C., September 29, 1966.

D. *Communications.* The Plan calls for utilization of the existing communication facilities of the D. C. Police, Fire, and Civil Defense Departments and the TV and news media.

E. *Notification.*

1. Police notify the Fire Department and Red Cross.

2. Fire Department will respond and evaluate the disaster. When necessary it will then mobilize disaster forces by notifying the District of Columbia Commissioners, Health Department, Office of Civil Defense, Department of Sanitary Engineering and of Highways and Traffic, Civil Air Patrol, D. C. Chapter of the American Red Cross, and the Medical Society of D. C. The Medical Society is to be notified by a call to the MEDICAL BUREAU 223-2200 when the Senior Police or Fire Surgeon or senior officer present decides that routine first aid would be inadequate. The MEDICAL BUREAU will then notify the Chairman of the Committee on Emergency Medical Service and the Captain of the MEDS.

F. *Disaster site.* The Plan is not specific as to individual functions at the disaster site but would provide the following medical aid:

1. Physicians from the Medical Society of D. C. No other agency has trained physicians to send.

2. Medical supplies from Civil Defense, Health Department, and Red Cross.

3. Nurses from Red Cross.

The chain of command at the disaster site is not specified but the Commissioner would probably delegate overall responsibility to the senior health officer on the scene. The health officer would delegate first aid and triage to the senior MEDS officer at the disaster and alert the community hospitals to put their disaster plans into effect.

The other D-I-S-A-S-T-E-R precept I should like to discuss is the S for supply of qualified physicians.

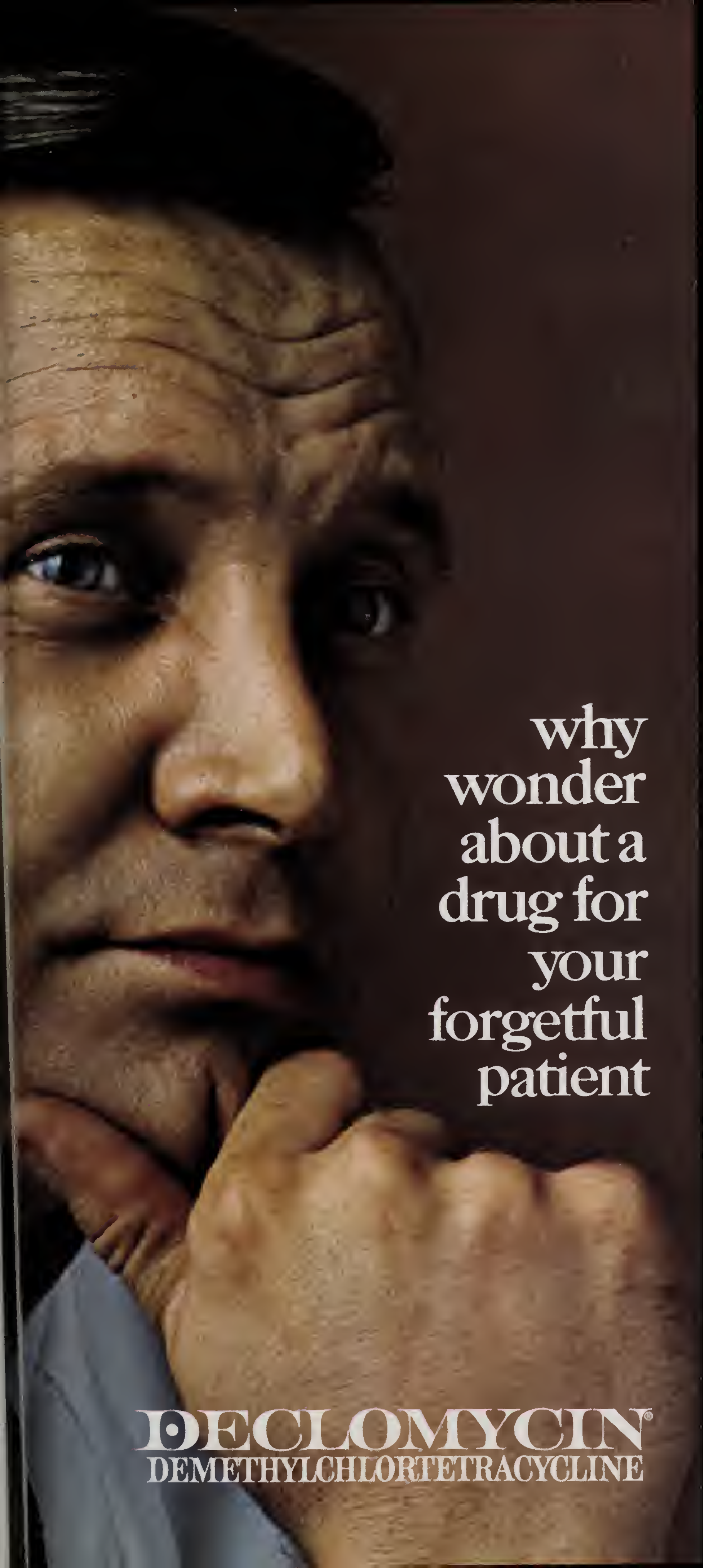
In time of disaster it is the local medical society which is called upon to supply physicians and surgeons for the care of unhospitalized sick and injured. Community hospitals cannot spare personnel for this function during disaster, and the Health Department, Civil Defense, Red Cross, and ambulance services, all of which have vital functions, cannot supply physicians. The National Guard and Armed Forces have efficient medical units available but their primary duties are military; they are not designed for community service and are under state or national command. They have provided great service in national emergencies, but because of the time it takes for them to become effective and the possibility that duty may call them elsewhere, they cannot be counted on in a community disaster. Neighboring communities have professional help, but they may have their own disaster or threat of disaster and be unwilling to leave. Reciprocal agreements should be formulated and included in practice alerts, but in reality each community must prepare to be self-sufficient.

The Committee on Emergency Medical Service of the Medical Society of the District of Columbia has a 2-point plan for the supply of professional manpower.

1. It has mobilized and trained volunteers from the Medical Society to supervise first aid and triage at the disaster site. Disaster and disaster exercises elsewhere have shown that the best medical care at the disaster site cannot be provided by ambulance corpsmen or residents and interns from community hospitals. This valuable community service is provided in the District of Columbia by the MEDS, captained by Dr. Ronald Strong. This concept originated in this committee of the District Medical Society and is being copied by other communities in the United States.

2. The second function of your Medical Society is to supply physician manpower through its MEDICAL BUREAU, which has a roster of over 1,000 community physicians, many of whom have no hospital disaster assignments.

In summary, "The Role of the Medical Society in Disaster" has been defined as one of preparedness, and the 8 D-I-S-A-S-T-E-R precepts of the Medical Society of the District of Columbia have been stated. The delegation of responsibility in the Natural Disaster Plan and the use of physician manpower during disaster in the District of Columbia have been elaborated in detail.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Effective in a wide range of everyday infections—respiratory, urinary tract and others—in the young and aged—the acutely or chronically ill—when the offending organisms are tetracycline-sensitive.

Contraindication—History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive systemic accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort.

Precautions and Side Effects—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. Use of demethylchlortetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long-term use but has also been observed in short treatment courses. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment. Side reactions include glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and dermatitis. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Anaphylactoid reactions have been reported.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products.

Capsules: 150 mg; *Tablets:* film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

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Health Dept. Notes

Hill-Burton Program

THE HILL-BURTON PROGRAM for construction of medical facilities marks its twentieth anniversary this year. It has become one of the more successful health programs in this country.

One reason for success is that the Hill-Burton program, from the first, called for a practical, working partnership among all who would be involved in it. The community's hospitals, physicians, the Federal Government, public health agencies, voluntary associations, and residents themselves were active participants in these efforts to improve medical facilities.

Since the program began there have been 26 separate projects approved for the District of Columbia. There are few hospitals, clinics, health centers, and other facilities in Washington which have not benefited from the program.

It has permitted Washington area residents to receive more and better care in more and better hospitals than would have been possible without it. It has permitted good hospitals to become better and has encouraged construction of needed health facilities.

The District of Columbia has received $8,355,000 since the Hill-Burton Act was passed 20 years ago. This has made possible the construction or expansion of $23 million in medical facilities here. It has provided for 628 new hospital beds, which is the equivalent of 1 large, new, modern hospital. But better still, these added facilities have been distributed throughout Washington in places where they are most needed.

It is acknowledged that the Hill-Burton

1946-1966
DEPARTMENT OF PUBLIC HEALTH
Government of the District of Columbia

THE TWENTIETH ANNIVERSARY of the Hill-Burton program for hospital construction was marked by ceremonies at the D. C. Department of Public Health, August 17. Dr. Murray Grant, D. C. Director of Public Health, was host at the ceremonies to a number of honored guests, including (left to right) Dr. William H. Stewart, Surgeon General of the Public Health Service; (Dr. Grant) Dr. Harald Graning, Chief of the PHS Division of Hospital and Medical Facilities; and Dr. Lawrence A. Rapee, Vice President of the D. C. Medical Society. Since 1946 over 8 million dollars has been allocated for the construction of hospital and health facilities in the District of Columbia, providing more than 600 additional hospital beds for its residents.

program has, in providing new equipment and facilities, served to improve the level of patient care. It has given the practicing physician a place and means for using his medical skills at their highest levels.

Some hospitals have used Hill-Burton funds to modernize their operating rooms. Some have installed facilities which they may not have had before, such as intensive care units or physical therapy sections. Some have renovated plumbing and electrical systems in older but still useful buildings.

Physicians who serve on hospital boards know that Hill-Burton has not been a government giveaway. Standards of construction, patient care, staffing and service were all to be met in what have been firm but reasonable requirements. This too has acted to upgrade medical care.

As the Hill-Burton program enters its third decade it finds the nature of need changed throughout the country. The program provides now for long-term care facilities (nursing homes and chronic disease facilities); for diagnostic, treatment and rehabilitation services; for community-wide planning; for modernization and renovation; and for research and demonstration purposes.

MURRAY GRANT, M.D., D.P.H.
D. C. Director of Public Health

Patients Needed For Study at Clinical Center

THE COÖPERATION OF PHYSICIANS is requested in the following studies being conducted by the National Cancer Institute at the Clinical Center of the National Institutes of Health in Bethesda, Md.

Diseases of Calcium Metabolism. Of interest for a continuing clinical study of calcium metabolism and calcium kinetics by the Metabolism Branch are patients with calcinosis universalis, hypoparathyroidism, hyperparathyroidism, pseudohypoparathyroidism, and hypercalcemia of malignancy without bony metastases. Patients with roentgenologic evidence of bone disease as well as documented serum calcium abnormalities would be of special interest.

Patients for this study should be clinically stable, ambulatory, continent of urine and feces, and be willing to participate in metabolic balance studies, including administration of Ca^{47}, during a 30-day admission to the Clinical Center.

Physicians interested in having their patients considered for this study may write or telephone Dr. James M. Phang, Clinical Center, Room 3B-40, National Institutes of Health, Bethesda, Md. 20014; telephone: 656-4000, Ext. 63097.

Chronic Lymphocytic Leukemia. Referrals of selected patients, particularly those with high circulating lymphocyte counts, are needed for a continuing study of chronic lymphocytic leukemia, including therapy in patients with this disorder, being conducted by the Medicine and Radiation Branches of the Institute.

Physicians interested in having their patients considered for the study may write or telephone Dr. Ralph E. Johnson, Clinical Center, Room B1B-41B, National Institutes of Health, Bethesda, Md. 20014; telephone: 656-4000, Ext. 65457.

Chronic Myelogenous Leukemia. For a continuing study of chronic myelogenous leukemia, being conducted by the Medicine Branch of the National Cancer Institute, referrals of patients with chronic myelogenous leukemia are needed. Patients of all ages with high white blood cell counts and platelet counts are needed for studies of newer chemotherapeutic agents and as a source of white cells and platelets for in vitro and in vivo study.

Physicians who wish to have their patients considered for the study may write or telephone Dr. Paul P. Carbone, Clinical Center, National Institutes of Health, Building 10, Room 12-N-228, Bethesda, Md. 20014; telephone: 656-4000, Ext. 64251.

Hodgkin's Disease. Particularly desired are patients who have had no previous treatment or minimal prior treatment. All clinical stages of biopsy-proven disease are acceptable. The major purpose of the study is to determine the curative potential of intensive radiotherapy in localized cases and to evaluate combination chemotherapy and X-irradiation in patients with generalized involvement.

Physicians interested in having their patients considered for the study may phone or write to Dr. Carbone.

Patients with Severe Pectus Excavatum

The coöperation of physicians is requested in a study of cardiac function in patients with a severe pectus excavatum chest wall deformity being conducted by the National Heart Institute at the Clinical Center.

Recent investigations suggest that cardiac function may be significantly impaired in some pa-

(*Continued on page 640*)

MEDICO, A Service of CARE*

MEDICO, FOUNDED in 1958 by Dr. Peter D. Comanduras of Washington and Dr. Thomas A. Dooley, became a service of CARE in 1962. It attempts to bring direct physician-to-patient medical aid to areas where the need is greatest, and to teach and train others to give better medical assistance. It promotes public health and, when requested, assists in family planning. Its various programs aim at developing an awareness of, and a sense of responsibility for, the basic problems of medical training and treatment on the part of responsible medical and government personnel. The complexity of the programs varies with the ability of the host country to utilize the training and equipment provided and to incorporate improved standards into the existing framework of medical care.

Facilities are made available by host governments from agreements entered into between Ministers of Health and CARE-MEDICO. The agreement provides for counterpart personnel to those being sent by MEDICO, for freedom from import duties on medicines and medical supplies shipped to the host country, and for free transportation for them within the country. The pharmaceutical and medical equipment manufacturers in the United States are most liberal in their donations of drugs and supplies for MEDICO's use.

Teams consist usually of 2 general practitioners, 1 for medicine and 1 for surgery; about 5 nurses, 1 of whom is an anesthetist and 1 trained in operating-room procedures; 1 X-ray technician and a laboratory technologist. They stay on their assignment for 2 years. Their expenses are met by MEDICO and they are given a small salary. MEDICO receives its funds for these costs and other overhead needs by direct donations to CARE or MEDICO. The amount of assistance rendered is dependent on donations received.

Teams are reinforced by visiting specialists who remain on site usually 1 month and pay all their own way. They have an income-tax privilege for their expenses as a donation to CARE-MEDICO. More than 500 such specialists have contributed their services during the past few years to MEDICO. A few have served in areas quite alone, where there were no permanent teams, and brought their specialty to a government hospital in conjunction with local physicians.

As progress is achieved, effort is transferred to other needier areas. Since inception, MEDICO has served in one form or another in Laos, Vietnam, Cambodia, Malaysia, Hong Kong, Afghanistan, Jordan, Tunisia, Algeria, Morocco, Kenya, Tanganyika, Gabon, Nigeria, Haiti, Colombia and Honduras. At this time there are 2 teams in Afghanistan with other teaching assistance being rendered in 2 medical schools; 2 teams in Algeria; 1 in Honduras, with a lecture program in a medical school; and 4 teams in Malaysia. Specialist coverage exists in these countries and in Jordan, Nigeria and Tunisia. The permanent teams are managed from the main offices of CARE in New York, while the specialist programs are handled in Washington's MEDICO office at 2007 Eye Street, N.W., telephone 223-2277.

By merging with CARE, advantages accrued constructively to both CARE and MEDICO. CARE, in its coöperative assistance and relief everywhere, has outstanding administrative men in about 50 countries who can relieve the physicians of many inherent managerial time-consuming problems. MEDICO gives to CARE a medical arm which was greatly needed. Overhead savings were tremendous.

Two of MEDICO's major programs were created in Washington. Orthopedics Overseas, built up by Dr. Allan M. McKelvie of this city, placed an orthopedist in Jordan each month. Two Jordanian surgeons were trained in orthopedics, a mass of corrective surgery brought the country to the level of the United States, while current trauma was handled, and the program came to a close with a mass polio immunization. Orthopedics Overseas now has programs in Tunisia, Nigeria, Afghanistan, Malaysia and Honduras. The International Eye Bank (now Foundation), which is credited with tremendous worldwide humanitarian work, has been under the guidance of Dr. J. Harry King since its inception. This work is so extensive it warrants an article unto itself.

The physicians of Washington are liberal donors of their skills to MEDICO's efforts. Their reports from their experiences in less privileged areas of the world are replete with heartrending appeals for further assistance where needs are real and are serious. They encounter difficulties unthougth of which challenge their professional abilities as well as their patience, but they are recognized as the finest ambassadors we can send abroad. MEDICO draws no lines as to race, creed or politics and, as such, wins many friends for this country. Each returning doctor and nurse usually states, "This has been the most satisfying experience of my life."

MAJOR GENERAL K. L. HASTINGS, USA (RET.)
Director of Professional Personnel, MEDICO

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* EDITOR'S NOTE: An increasing number of groups are now offering medical assistance to foreign countries. In order to keep our members informed of their current activities and needs, we are publishing a series of articles submitted by such groups, of which this is the second.

MOLECULAR REMODELING–

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis–a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect–metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors –in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'–an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase–it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic–an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9, 10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

Naturetin–effective diuresis with more favorable electrolyte balance

Other thiazides followed – with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide…"[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.

Contraindications: Severe renal impairment; previous hypersensitivity.

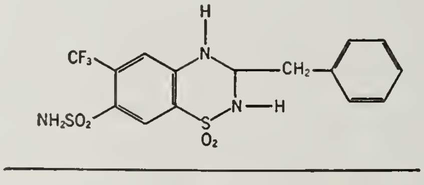
Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

References: **1.** Southworth, H.: Proc. Soc. Exper. Biol. & Med. *36*:58, 1937. **2.** Mann, T. and Keilin, D.: Nature *146*:164, 1940. **3.** Pitts, R. F., and Alexander, R. S.: Am. J. Physiol. *144*:239, 1945. **4.** Schwartz, W. B.: New England J. Med. *240*:173, 1949. **5.** Friedberg, C. K., in Moyer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia, W. B. Saunders Co., 1960, p. 259. **6.** Cumming, J. R.; Tabachnick, E., and Seelig, M., in Moyer, J. H., and Fuchs, M.: op. cit., p. 254. **7.** Werko, L., in Moyer, J. H., and Fuchs, M.: op. cit., p. 188. **8.** Beyer, K. H., Jr., in Moyer, J. H., and Fuchs, M.: op. cit., p. 274. **9.** Maren, T. H., and Wiley, C. E.: J. Pharmacol. & Exper. Therap. *143*:230, 1964. **10.** Earley, L. E., and Orloff, J.: Ann. Rev. Med. *15*:149, 1964. **11.** Fuchs, M., and Mallin, S. R., in Moyer, J. H., and Fuchs, M.: op. cit., p. 276. **12.** Ford, R. V., in Moyer, J. H., and Fuchs, M.: op. cit., p. 290. **13.** cited in Fuchs, M., and Mallin, S. R. (ref. 11): op. cit., p. 283.



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Veterans Administration Investigation on Aging

Growing old is simply a question of mind over matter—if you don't mind, it doesn't matter. That is the consensus of researchers in the psychology of aging at the Veterans Administration hospital in Houston, Texas.

Regardless of their age, persons who are effective and productive do not think of themselves as growing old. Apparently they are not aware that they are aging.

In sharp contrast, the researchers observed that individuals who have difficulty in their adaptation to later life tend to occupy themselves with thoughts of growing old even while they are relatively young.

Of the 165 VA hospitals, 38 hospitals and a number of outpatient clinics are conducting research programs in this field. Special laboratories for aging research are established in 7 VA hospitals. Thirty-two coöperative studies, involving 3 to 30 hospitals each, are directly related to the research.

A program of "satellite laboratories" nourishes new concepts in the problems of aging. In these the VA is obtaining the coöperation of a distinguished group of scientists and physicians who are not otherwise associated with the Agency. To them the VA offers facilities and staff assistance in nearby VA hospitals for the advance of their own ideas for research.

Six of these VA satellite laboratories operate at Bedford, Mass., Baltimore, Md., Downey, Ill., Buffalo, N. Y., and 2 at Sepulveda, Calif. Ten additional satellite laboratories are planned.

Concerned with the physical aspects of aging, researchers at the Sepulveda VA hospital observed a progressive enlargement of the heart and changes of metabolism during the aging process. They noted a decrease in protein albumin carried to the heart muscle and a decrease in hyaluronic acid present in organs having an increasing amount of connective tissue.

The loss of hyaluronic acid would account for many of the characteristics associated with aging, they contended. In the animal laboratory they were able to demonstrate an increase in albumin and hyaluronic acid in the vital organs following the administration of the female hormone estrogen.

While an expected increase has occurred in the number of patients suffering from the chronic diseases which affect older persons, the VA hospitals have had an increase of 33 per cent in the number of arteriosclerotic heart disease patients, and an increase of 50 per cent in the number of patients suffering strokes and other brain damage accompanying aging.

Efforts have been intensified in the investigation of heart disease, strokes, emphysema, cancer, diabetes, rheumatism and mental illness. Emphasis is being placed upon new ideas and new approaches to the multitude of problems presented by aging and the increasing population of senior citizens.

Certain complex body sugars called mucopolysaccharides (MPS) always decrease with age, according to research workers at the VA hospital in West Roxbury, Mass. They also found an increased resistance to drying by the MPS while the water content decreased with age.

Three major studies now under way represent the scope of the VA research in aging. A long-term study of the aging process in healthy men was launched by the VA outpatient clinic at Boston. It will delineate selective anatomic, biochemical, physiologic, and psychosocial aspects of aging in 1,500 initially healthy men ranging in age from 25 to 65 years. The subjects volunteer to return for periodic examinations for the rest of their lives.

This study is expected to provide descriptions of the normal aging processes, prediction of later outcomes, and correlation of variables. The subjects were screened for normality and will return for extensive examinations at intervals of 3 to 5 years. Each test series comprises about 15 hours of examination.

Knowledge gained from the VA research programs in aging will be used to provide better treatment for illnesses which beset senior citizens and will be used to make their lives more comfortable and more productive.—*News release, Veterans Administration, June 23, 1966.*

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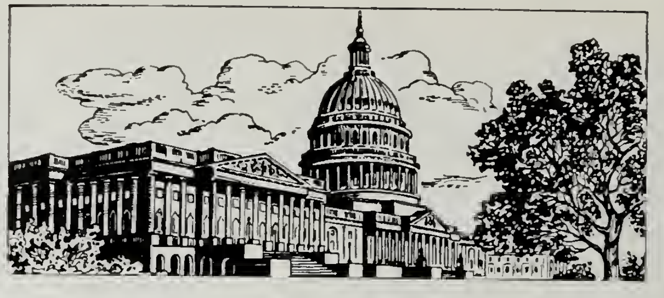

NEWS & PERSONALS

Summary of Executive Board Actions

Proceedings of August 29 Meeting

Dinner for the members of the Executive Board was served at 6:30 p.m. in the Exhibit Hall of the Medical Society of the District of Columbia, August 29, 1966. Dr. J. Spencer Dryden, Chairman, presided at the meeting. Present were Drs. Robert J. Coffey, Karl C. Corley, Henry D. Ecker, Claudine M. Gay, Raymond T. Holden, Edward W. Nicklas, Paul R. Wilner, and Mr. George W. Cooley, Secretary. Also present was Dr. William H. Cooper, Chairman of the Board of Directors, DOCPAC, and Mr. Warren Magee, legal counsel. The meeting was called to order at 7:00 p.m.

The minutes of the meeting of July 25, which had been mailed previously, were approved.

Committee Meetings: The following committee meetings were reported by the Secretary as having been held since the Board last met:

July 28	Committee on Insurance
August 3	Fee Review Committee
16	Grievance Committee
17	Board of Credentials

Board of Credentials: On recommendation of the Board of Credentials, the following applicants for membership and changes in membership status were approved:

Active Members

Kristof Abraham, National Institutes of Health, Bethesda, Md.
James Albert Austin, 825 New Hampshire Avenue, N.W.
Mathias John Coleman, 2025 Eye Street, N.W.
Arthur Roy Henderson, 7600 Georgia Avenue, N.W.
Perry Hookman, D. C. General Hospital
Russell Lee Hughes, 1835 Eye Street, N.W.
Ramon Barton Jenkins, Children's Hospital
Myron Koch, 1918 K Street, N.W.
Oscar Mann, Georgetown University Hospital
Ernest Douglass Martin, 1603 Rhode Island Avenue, N.E.
James Edward McClenathan, Children's Hospital
Pedro Mario Pabon, Morris Cafritz Memorial Hospital
Robert Earl Pumphrey, Jr., 1150 Connecticut Avenue, N.W.
Stanley Alvin Schwartz, 2400 H Street, N.W.
Robert Lawrence Simmons, Freedmen's Hospital
Harold B. Zimmerman, Georgetown University Hospital

Associate Members

Neilson T. Devevoise, U. S. Naval Hospital, Bethesda, Md.
Martin H. Eichler, 911 Silver Spring Avenue, Silver Spring, Md.
Dennis John Hand, George Washington University Hospital

Resident-Intern Members

Bernard Ehrlich, George Washigton University Hospital
David Raymond Notes, 7809 16th Street, N.W.

Reinstatements

Active: Vernon H. Balster and Roy Hertz
Associate: S. P. Feldstein and John P. Nasou

Transfers

Active to Associate: William F. Burdick, Jacob Ceppos, Bernhard J. F. Kramer, and Neville Ottley.
Associate to Active: George Szele
Resident-Intern to Associate: Giulio Italo Scarzella

Resignations

Active: John G. Hewitt
Associate: Robert L. Bregman, Charles S. Christianson, Lucienne Numa, John C. Watson, and Frank J. Weinstock
Resident-Intern: Edward W. Walters

On recommendation of Dr. Camalier, the Board voted to invite Dr. William H. Stewart, Surgeon General of the United States Public Health Service, to become an Honorary member of the Medical Society of the District of Columbia.

The membership dues of Dr. Robert B. Hightower, which have been remitted since 1964 because of disability, were remitted indefinitely until Dr. Hightower notifies the Board that his situation has changed.

Dr. John F. Preston was invited to become a Special member in view of his almost total retirement and the fact that he has been a member of the Society for more than 30 years.

District of Columbia Political Action Committee: Dr. Cooper and Mr. Magee reported briefly on the activities of DOCPAC. Dr. Cooper pointed out that one of the problems was to obtain more interest in DOCPAC on the part of local physicians, particularly since the organization was bipartisan and interested primarily in political measures affecting the medical profession. Mr. Magee pointed out that some 33 states include the PAC dues, to be paid on a voluntary basis, in the membership dues statements of the societies. As legal counsel for this Society, he stated that he saw no objection to this method suggested by Dr. Cooper. It was voted to postpone action until the Secretary could present to the Board policy statements from the minutes of the Executive Board.

Interest in Drug Repackaging Companies: The Secretary reported on an article from *The Washington Post* which listed the names of physicians who owned stock in a repackaging firm in Virginia. The following policy statement from Opinions and Reports, Item 42, page 51, of the AMA Judicial Council was read: "It is unethical for a physician to have a financial interest in a drug repackaging company."

In defining a drug repackaging company, the House of Delegates "refers to a drug company which markets under its own label or trade names drug products manufactured by others with the objective that physicians having a financial interest in the drug company will prescribe its drugs to the patient."

It was voted to publish these 2 items from the Judicial Council in the Newsletter together with the action taken at the AMA meeting in June 1966 regarding the dispensing of drugs.

Committee on Regional Medical Programs: Dr. Coffey reported that the application for a planning grant had been submitted and was looked upon favorably by the Advisory Committee at the National Institutes of Health. Dr. Marsten asked for a conference with representatives of the Society's Committee on Regional Medical Programs for Monday, October 3, at 10 a.m. at NIH.

The Board expressed its appreciation to Dr. Coffey and to Dr. Desmond S. O'Doherty for their efforts in developing this program.

Low Cost Drug Program: The Secretary reported on a program sponsored by the D. C. Health Department, the D. C. Pharmaceutical Association, the D. C. Medical Society, the Washington Heart Association, and the Medico-Chirurgical Society of D. C. to provide at reduced cost penicillin as a prophylactic measure to rheumatic heart disease patients. The final meeting is set for September 22. The program will start November 1. Private doctors will determine who is to receive the drug at reduced cost.

Income and Expenses: A statement of income and expense for the first 6 months of 1966 as compared with the same period in 1965, previously mailed to the Board members, was reviewed and approved as submitted.

Committee on Insurance: Action on the proposed Retirement Program available through the Variable Life Insurance Company was postponed with the request that data on the proposal be forwarded to the Executive Board.

The Group Life Insurance Program for Society members, underwritten by the Mutual Benefit Life Insurance Company, was approved for presentation to the membership in September.

Miscellaneous Business

The Secretary referred to a memorandum previously sent to the Executive Board which recommended Dr. James J. Feffer for membership on the Committee on Insurance and Prepayment Plans of the AMA's Council on Medical Service. Since most Board members had replied in the affirmative, the Secretary stated that this recommendation had been mailed to the Chairman of that Committee.

The Secretary reported that Dr. Yuill Black has agreed to replace Dr. Eloise W. Kailin in checking the pollen count each day and then reporting to the news media. This change was approved by the Executive Board with instructions that the Secretary report it in the Newsletter to the membership and express the Board's appreciation to Dr. Black.

The Secretary reported briefly on 3 news releases, 2 of which had received publicity in the newspaper and on television. These concerned Title XIX of P.L. 89-97, the Air Pollution Statement of the Committee on Environmental Health, and "cigarette smoking in hospitals." The latter, which had not yet been released, was approved for release to all hospitals in the District.

A letter from the Planned Parenthood Association requesting permission to participate in Community Health Week was read and such participation was approved.

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A letter from Dr. Earl H. Mitchell requesting participation by the Society in a 1-day Institute on Alcoholism, to be sponsored by the Washington Area Council on Alcoholism and the Pastoral Institute, was read and such participation by the Society was approved.

A memorandum was read in which Dr. Thomas E. Reichelderfer requested participation by the Medical Society in an educational program on pediatrics to be held at D. C. General Hospital, and participation in this program was approved.

Dr. Coffey reported briefly on the present status of the GHI-Hospital Council controversy and was authorized to use his judgment in reinstating negotiations with these 2 groups if an agreement is not reached within a reasonable length of time.

Dr. Holden reported to the Executive Board on the action of the AMA House of Delegates in reference to the ethical status of a physician who accepted a position with a hospital where his predecessor had been released because of his determination to bill separately. He pointed out that the Board of Trustees of the AMA had later voted that Resolution 104 on separate billing for professional services by hospital-based physicians, adopted by the House of Delegates in June 1966, not be implemented by the AMA and that a letter be directed to the delegates, alternate delegates, and others explaining the action of the Board and recommending that the resolution not be implemented at the state or local level.

Meetings

The Annual Business Meeting of the Medical Society of the District of Columbia will be held in the Exhibit Hall of the new Medical Society Headquarters at 2007 Eye Street, N.W. on Sunday, November 20, at 4 p.m. Dr. Robert J. Coffey, President of the Society, will preside. Annual Reports will be presented by the Chairman of the Executive Board, the Chairman of the Board of Credentials, and the Secretary-Treasurer of the Society. There will be election of officers for 1967 and presentation of annual awards.

A National Conference on Air Pollution, sponsored by the U. S. Department of Health, Education, and Welfare, will be held at the Sheraton-Park Hotel, Washington, December 12–14.

Under the theme, "Control Now for Clean Air," the Conference will evaluate progress made in controlling air pollution since the previous Conference held in December 1962 and will determine what steps should now be taken to accelerate the national effort to control the problem. Conference participants will include physicians, engineers, scientists, legislators, control officials, and representatives of business, labor, and civic organizations. The meetings will be open to the general public.

Additional information may be obtained by addressing the Executive Secretary of the National Conference on Air Pollution, Public Health Service, U. S. Department of Health, Education, and Welfare, Washington, D. C. 20201.

The Council on Medical Service and the Division of Socio-Economic Activities of the American Medical Association will sponsor **the First National Congress on the Socio-Economics of Health Care,** January 22–23, 1967 at the Palmer House, Chicago. The Congress will bring together authorities from medicine, health care administration, social science, education, community planning, and other disciplines to report on new issues, developments and techniques in the organization, delivery and financing of health care

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Side Effects: Hypersensitivity reactions including skin rashes, urticaria, hypotension and thrombocytopenia have been reported on rare occasions. Drowsiness, lassitude, nausea, giddiness, dryness of the mouth, mydriasis, increased irritability, or excitement may be encountered.

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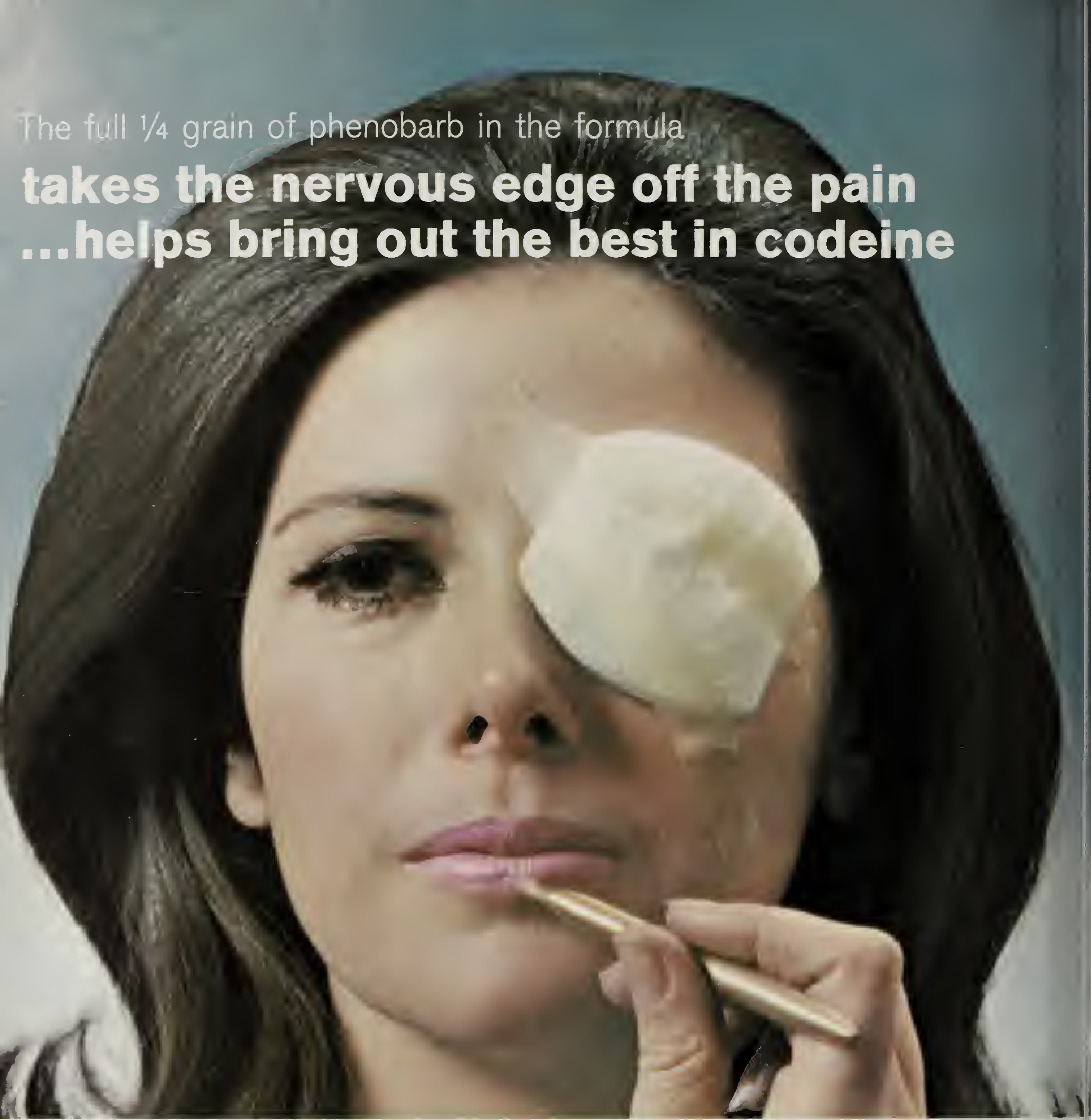
*Schiller, I. W., and Lowell, F. C: New England J. Med. 261:478, 1959.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Phenacetin (3 gr.) ....194.0 mg.
Hyoscyamine sulfate..................0.031 mg.
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½ gr. (No. 3), 1 gr. (No. 4)
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Precautions: As with all phenacetin-containing products, avoid excessive or prolonged use.

Side Effects: Side effects are uncommon—nausea, constipation, and drowsiness have been reported.

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services. For more information, write to Dr. H. W. Doan, Secretary, Council on Medical Service, American Medical Association, 535 North Dearborn Street, Chicago, Ill. 60610.

The First Annual Clinical Meeting of the Society for Cryo-Ophthalmology will be held at the Dunes Hotel, Las Vegas, January 8–10, 1967. The clinical aspects of cryo-ophthalmology will be stressed, including cataract, glaucoma, retinal detachment, and herpetic keratitis. A $10 registration fee will include a year's membership in the Society. Further information may be obtained from Dr. John G. Bellows, 30 North Michigan Avenue, Chicago, Ill. 60602.

General News

The Food and Drug Administration has named **Dr. Herbert L. Ley, Jr., as Director of its Bureau of Medicine,** effective September 19. He succeeds Dr. Joseph F. Sadusk, who resigned last March. Dr. Ley, a graduate of Harvard Medical School, has been Associate Professor of Epidemiology and Microbiology at the Harvard School of Public Health since 1963. He was Professor of Bacteriology at George Washington University from 1958 to 1961, and from 1961 to 1963, Chief of the Biological and Medical Sciences Branch of the Army Research Office in Arlington, Va.

Dr. Francis L. Land, of Fort Wayne, Ind., has been **appointed Medical Consultant to the Commissioner of Welfare** in the Department of Health, Education, and Welfare. His assignment, a new one, effective September 6, will encompass the medical aspects of Title XIX of Medicare, which provides medical and dental assistance for indigent persons under 65 and children.

Dr. Land is Vice President of the American Academy of General Practice. In 1962 he served as President of the Indiana Academy of General Practice. He was elected to the AMA's Council on Medical Education in 1963 and the following year was appointed a consultant in general practice to the Air Force. He is a graduate of Indiana University School of Medicine.

Dr. Karl C. Jonas has been **appointed Chief of Surgery of Doctors Hospital Medical Center,** effective September 5. He comes to Washington from Philadelphia, where he was Chief of Surgery at St. Joseph's Hospital, Senior Attending Surgeon at West Park Hospital, and Director of Surgery at Stetson Hospital. He received his medical degree from Duke University School of Medicine and the degree, Master of Science in Surgery, from Temple University. In addition to his position as Chief of Surgery at Doctors Hospital he will be engaged in the private practice of surgery.

Anagnos Memorial Fund

A TRUST FUND is being established for the family of Dr. S. George Anagnos by several of his colleagues, to be administered by the Medical Society of the District of Columbia. Physicians wishing to contribute should make their checks payable to the Medical Society of the District of Columbia, designating the Anagnos Fund, and mail to the Medical Society, 2007 Eye Street, N.W., Washington, D. C. 20006.

Dr. Jonas is editor of a surgical textbook, "Babcock's Principles and Practice of Surgery," and he has published numerous articles in professional surgical journals.

Dr. William Haddon, Jr., was appointed by President Johnson in September **to head up the new Traffic Safety Agency** created under P.L. 89-564. Dr. Haddon holds an engineering degree from the Massachusetts Institute of Technology, and he received his medical degree from Harvard University. He has been the Special Assistant for Traffic Safety Planning to the Under Secretary of Commerce. His new title will be Highway Safety Administrator of the Traffic Safety Agency of the Department of Commerce, which carries the rank of Under Secretary.

A Chair in Pharmacology has been established at Georgetown University through funds made available by the Schering Foundation of Bloomfield, N. J. The Reverend Gerard J. Campbell, S.J., President of Georgetown, in accepting the gift for the University, stated: "This Chair will provide in perpetuity for the teaching services of a leading pharmacological scholar and staff assistants in a vital area of the health sciences at a time when this country faces an incredible expansion in health care." He also noted that the Chair is the first in Georgetown's 177-year history.

An informative folder, "Plastic Surgery," has been developed by the American Academy of

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The D. C. Allergy Society elected the following officers at its meeting at the Walter Reed Officers' Club, September 29:

Dr. Halla Brown, *President*; Dr. Roland B. Scott, *President-elect*; Dr. Robert T. Scanlon, *Secretary-Treasurer*; and Drs. Ellis April and Solomon E. Barr, *members of the Executive Committee.*

New officers of the **Washington Orthopedic Club** for 1966–67 are:

Dr. Charles Keck, *President*; Dr. Everett J. Gordon, *Vice President*; and Dr. Charles H. Epps, Jr., *Secretary-Treasurer.*

The D. C. Medical Society coöperated with the District Department of Public Health in conducting a 1-week course, the week of September 12, in **Radiological Health for Senior X-ray Technologists.** The Radiological Health Laboratory of the Public Health Service at Rockville, Md. provided the facilities and the instructional staff.

The 21 technologists who participated represented the following hospitals: Arlington, Morris Cafritz Memorial, Children's, D. C. General, Freedmen's, Glenn Dale, George Washington, Leland Memorial, Saint Elizabeths, Veterans Administration, Walter Reed General, and the Washington Hospital Center. Technologists were also present from the D. C. Department of Public Health, Group Hospital Association, and from the radiological firm of Groover, Christie & Merritt.

The U. S. Air Force has named the hospital at Travis Air Force Base, Calif. in honor of the late **Dr. David N. W. Grant** as a living memorial to the man who first conceived the idea of mass evacuation of wounded by air during World War II. After a distinguished career in the military, retiring as the Air Surgeon of the Army Air Force, with the rank of Major General, Dr. Grant served as National Director of the American Red Cross Blood Program from 1951 to 1956.

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[1] Riese, J. A.: Amer. J. Gastroent. 28:541 (Nov.) 1957

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Rebecca Sweeney, R.N., Director of Special Services of the Washington, D. C. Tuberculosis Association, has retired after 21 years with the Association. She came to the Association in 1945 after having served with the D. C. Visiting Nurses Association, Children's Hospital, and the D. C. Department of Public Health. In 1964 she was the recipient of the Funkhouser Memorial Award for distinguished service in public health.

Personals

Dr. William S. Anderson was installed as President of the American Academy of Pediatrics during the 35th Annual Meeting of the Academy in Chicago, October 22–27.

The D. C. Board of Commissioners has appointed **Dr. John W. Latimer, Jr.** to the Board of Appeals and Review for a term expiring April 30, 1969. He succeeds Dr. Samuel Hazen Shea, whose term has expired.

DR. ROBERT J. COFFEY (right), President of the District Medical Society, proudly displays the Georgetown University Medical Center Number (September) of the MEDICAL ANNALS which was dedicated to him in recognition of his able administration of the Department of Surgery at Georgetown which he heads. Among those gathered in the Medical Society lounge at a small informal party in his honor, September 8, were (left to right) Dr. Wallace M. Yater, Editor of the ANNALS; Dr. Irving B. Brick, Professor of Medicine at Georgetown; Dr. Henry D. Ecker, President-elect, and Dr. J. Spencer Dryden, Chairman of the Executive Board, of the Medical Society.

Dr. Oscar B. Hunter, Jr., Director of the Hunter Memorial Laboratory at Doctors Hospital, has been elected President-elect of the College of American Pathologists. Dr. Hunter is also Director of Pathology at Sibley Memorial and Montgomery County General Hospitals and is on the faculty of Georgetown University School of Medicine as Professorial Lecturer in Forensic Medicine. The election took place during the annual meeting of the pathologists at the Washington Hilton Hotel, September 17–23.

Dr. Hunter, President-elect of the College of American Pathologists

Dr. Bernard R. Cooperman was designated the official representative of the American Medical Association to the Medical Week of Paris, which was held in Paris, October 2–9, 1966.

Dr. Julius Fogel has been elected President of the Reserve Officers Association of the U. S. Public Health Service.

Dr. Fogel was recently elected to fellowship in the American College of Obstetricians and Gynecologists.

Dr. Harvey H. Ammerman, who has long been affiliated with Sibley Memorial Hospital, was elected to the Board of Trustees of the Hospital on May 13. Dr. Ammerman initially served as an extern at the Hospital in 1942. He became a member of its active staff in 1951 and Chief of the Section of Neurological Surgery in 1955, which position he still holds.

Dr. Luther L. Terry, Vice President for Medical Affairs at the University of Pennsylvania, has been elected Chairman of the National Interagency Council on Smoking and Health as of January 1, 1967. Dr. Terry, formerly Surgeon General of the Public Health Service, is an Honorary member of the D. C. Medical Society.

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Dr. Leon Salzman has been cited as "Man of the Month" by *Pastoral Psychology* for his "interest in the field of religion and mental health, and particularly for his contributions to the psychological understanding of religious conversion."

Dr. Salzman has been Professor of Clinical Psychiatry at Georgetown University School of Medicine since 1960. He is a charter member and President of the Academy of Psychoanalysis and a member of the Board of Directors of the Washington School of Psychiatry. His first study of "religious and ideological conversion" was published in *Psychiatry* in 1953.

On Wednesday, September 21, **Dr. R. Lomax Wells**, Chairman of the AMA Council on Occupational Health, and General Medical Director of the Chesapeake and Potomac Telephone Companies of Washington, testified for the American Medical Association on H.R. 16920 and S. 3722, Recordkeeping for Radiation Workers, before the Joint Committee on Atomic Energy. Dr. Wells spoke in opposition to these bills, stating that they are "narrowly focused on a relatively insignificant area of workmen's compensation. The Association objects to a system of recordkeeping which could place confidential medical records in the public domain or in any way violate their confidential nature. It also opposes those portions of the bill that would place varying state statutes under a single Federal standard. . . ."

Letters to the Editor

Dedicatory Issue to Dr. Coffey

Thank you very much for the September issue of the MEDICAL ANNALS OF THE DISTRICT OF COLUMBIA, which is dedicated to Dr. Robert J. Coffey, President of the Medical Society of the District of Columbia and Chairman of the Department of Surgery at Georgetown University. I am very pleased to see the tribute which is therein given to Dr. Coffey. I think it is especially fitting that the scientific articles were contributed by the members of the Department of Surgery, which is under Dr. Coffey's supervision.

We are, of course, very proud of his many achievements and we were especially happy that the physicians of the District of Columbia recognized his personal and professional achievements by choosing him as President of the Medical Society of the District of Columbia.

With best personal wishes, I am

Sincerely yours,
GERARD J. CAMPBELL, S.J.
President, Georgetown University

Obituaries

Socrates George Anagnos, M.D.

(1920–1966)

DR. S. GEORGE ANAGNOS, a specialist in internal medicine, died at the Washington Hospital Center, September 24, 1966. His offices were located at 1150 Connecticut Avenue, N.W.

Dr. Anagnos was born in Englewood, N.J., October 29, 1920. During World War II he served as a noncommissioned officer in the Medical Department of the U. S. Army. He received his premedical training at the University of Athens, Greece, and his medical degree in 1950 from the University of Geneva, Switzerland. He interned at old Emergency Hospital in Washington for a year and spent 3 years, 1952–1955, as resident physician in internal medicine at Emergency (now a part of the Washington Hospital Center).

In addition to his private practice, he served as a staff physician at the Washington Hospital Center.

He was elected to Active membership in the D. C. Medical Society in 1955. He also was a member of the American Medical Association.

He is survived by his wife, Mrs. Adrienne Anagnos, a son, Damon, and a daughter, Lydia, all of the home address, 8504 Thornden Terrace, Bethesda, Md.

James Irving Boyd, A.B., M.D., M.S.

(1898-1966)

DR. JAMES I. BOYD, medical examiner of Prince George's County, Md., died, July 31, 1966 at Doctors Hospital in Washington. He had been ill for a number of years.

Dr. Boyd was born in New York City, May 19, 1898, to Samuel and Jane Sparrow Boyd. He grew up in the District of Columbia, where he attended the elementary schools and Emerson Institute. From George Washington University he received 3 degrees, Bachelor of Arts (1922), Doctor of Medicine (1926), and Master of Science in chemistry in 1927. He interned for a year at George Washington University Hospital and was a resident there in 1928.

Dr. Boyd began practice in Maryland in 1929. He served 2 terms (1935 and 1936) as President of the Prince George's County Medical Society. In the late 1930's he was pathologist for Charles

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County and later examining physician for the Prince George's County Selective Service Board. He had served as Prince George's County Medical Examiner since 1944.

He was a member of the American Medical Association, the Southern Medical Association, and the George Washington University Medical Society. Elected to Associate membership in the Medical Society of the District of Columbia in 1938, he resigned in 1953. He was a member of the Board of Directors of the National Bank of Southern Maryland.

He leaves his wife, Mrs. Agnes Boyd, of the home, 8200 Marlboro Pike, Forestville, Md.; 2 daughters, Mrs. Kenneth Pruden, of Croome, Md., and Mrs. Harvey H. Nicholson, of Forestville, Md. He also leaves a sister, Mrs. E. E. Quayle, of Washington, and 2 brothers, John S. Boyd, of Hatboro, Pa., and Samuel Boyd, of Chevy Chase, Md.

Robert P. Grant, A.B., M.D.

(1915-1966)

Dr. Robert P. Grant, Director of the National Heart Institute in Bethesda, Md., died, August 15, 1966. He lived at 9301 Parkhill Terrace, Bethesda.

Dr. Grant, a native of Ontario, Canada, was born, September 17, 1915. He received his Bachelor of Arts degree from Cornell University and his degree in medicine from Cornell University Medical College in 1940. He interned and served as an assistant resident at Peter Bent Brigham Hospital in Boston from 1940 to 1942 before joining the Army Medical Corps in World War II.

He joined the Public Health Service in 1950 and was assigned to the Heart Institute in Bethesda until he left for Europe in 1962 to serve as Chief of NIH's European Office of International Research in Paris. He returned to Bethesda last March to take over the directorship of the Heart Institute.

Dr. Grant was a member of the American Heart Association, the American College of Cardiology, the American Federation for Clinical Research, and the Society for Clinical Research. He was certified in cardiology by the American Board of Internal Medicine. He was the author and coauthor of several books on the heart and was a member of the editorial board of 3 medical journals, *Circulation*, *Excerpta Medica*, and *Malattie Cardiovascolari*.

Functioning Carcinoid Tumor—Mattingly et al

(*Continued from page 584*)

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Sickle-cell Anemia—Surana, Scott and Ferguson

(*Continued from page 595*)

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Patients Needed for Study at Clinical Center

(*Continued from page 624*)

tients with this type of chest deformity. If further study verifies these results, such patients may be candidates for operative correction.

Referrals would be appreciated of any patient over 16 years of age who has a severe pectus excavatum deformity and who complains of excessive fatigue and exertional dyspnea.

Physicians interested in having their patients considered for admission to the Clinical Center for this study may write or telephone Dr. Stephen Epstein, Clinical Center, Room 7-B-14, National Institutes of Health, Bethesda, Md. 20014; telephone: 656-4000, Ext. 63015.

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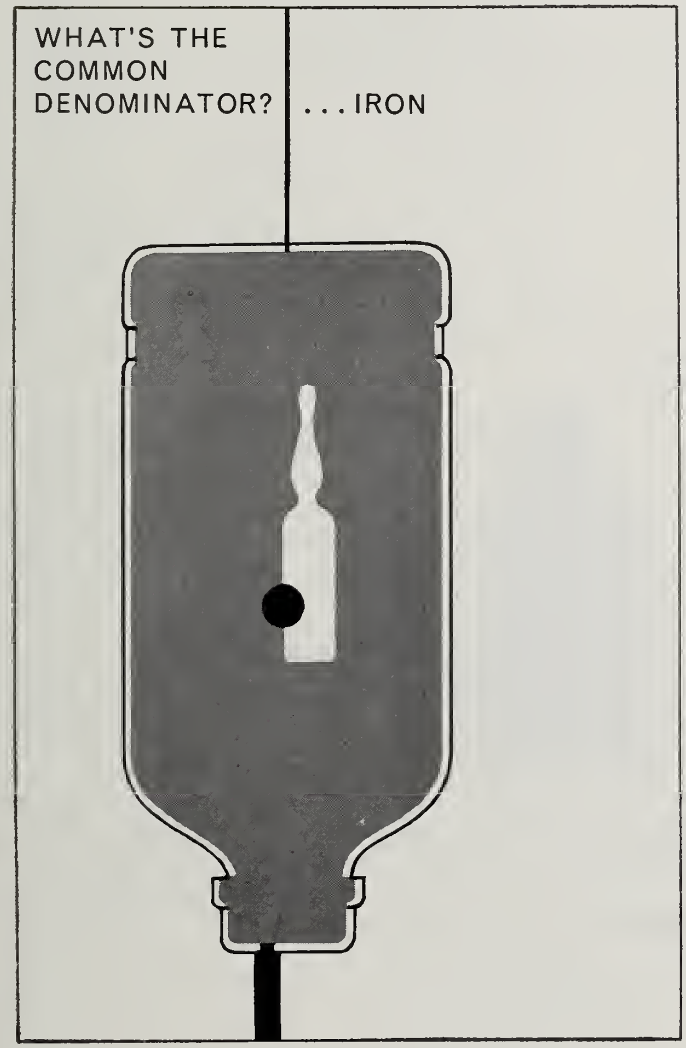

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ADMINISTRATION AND DOSAGE: Dosage, based upon body weight and Gm. Hb/100 cc. of blood, ranges from 0.5 cc. in infants to 5.0 cc. in adults, daily, every other day, or weekly. Initial test doses are advisable. The total iron requirement for the individual patient is readily obtainable from the dosage chart in the package insert. Deep intramuscular injection in the upper outer quadrant of the buttock, using a Z-track technique, (with displacement of the skin laterally prior to injection), insures absorption and will help avoid staining of the skin. A 2-inch needle is recommended for the adult of average size.

SIDE EFFECTS: Local and systemic side effects are few. Staining of the skin may occur. Excessive dosage, beyond the calculated need, may cause hemosiderosis. Although allergic or anaphylatoid reactions are not common, occasional severe reactions have been observed, including three fatal reactions which may have been due to Imferon (iron dextran injection). Urticaria, arthralgia, lymphadenopathy, nausea, headache and fever have occasionally been reported.

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BOOK REVIEWS

Current Diagnosis: A Biennial Volume of Clinical Diagnostic Methods and Evaluations. Edited by HOWARD F. CONN, M.D., ROBERT J. CLOHECY, M.D., AND REX B. CONN, JR., M.D. Price, $19.00. Pp. 843, illustrated. Philadelphia: Saunders, 1966.

This new book, edited by 3 physicians, is a first in this type of presentation of the subject. Some 225 authors have been enlisted in its preparation, all authorities in the many diseases discussed. It is astounding to this reviewer that the editors have been able to procure so many participants in this worthy effort. The subheadings are well selected and adhered to throughout (synonyms, definition, presenting signs and symptoms, course, physical examination, etc.). In the front and back of the book are tables of "Normal Laboratory Values of Clinical Importance." It is a good book.

This is a worthy companion book to "Modern Therapy," published also by Saunders and edited by Dr. Howard F. Conn. Can they keep it up?

ARTHUR BURGERMAN, M.D.

Arteriography: Principles and Techniques. Emphasizing Its Application in Community Hospital Practice. JOSEPH L. CURRY, M.D., AND WILLARD J. HOWLAND, M.D. Price, $14.00. Pp. 328, with 223 illustrations. Philadelphia: Saunders, 1966.

According to the authors, the "real purpose" of this monograph is to provide a brief introduction to the field of arteriography for physicians who need these diagnostic procedures performed in their own hospitals. This is a concise, clearly written, and beautifully illustrated text which fulfills its "real purpose," and in addition it summarizes the fantastic advances that have been made in the field of arteriography, which may aid general practitioners in the diagnosis and treatment of their patients. For the general surgeons this text will serve as an excellent "how-to-do-it" book, to be utilized when more experienced and sophisticated services in this field are not available in their time of need.

Beginning with the first 3 chapters, which deal with and describe essential equipment, techniques, pitfalls, complications and treatment, the authors then advance in a step-by-step manner, in the ensuing chapters, to describe the various techniques of specialized arteriography that are now available. Beginning with abdominal aortography and ending with surgical and postmortem aortography, the authors present an exhaustive synopsis of arteriography. The section on scanographic extremity arteriography, a new, simple, and highly successful technique, will be particularly rewarding to those peripheral vascular surgeons who are disenchanted with the "guesstimate" technique of timing run-off exposures.

In addition to an explicit description of technique, each chapter contains clear and concise indications, applications, and complications for the contemplated procedures, a résumé of the authors' experiences in these procedures, and up-to-date bibliography, and excellent illustrations of the pathology.

Although it is admittedly weak in the more advanced techniques of coronary angiography, this treatise is broad enough in scope and exhaustive enough in detail to satisfy adequately the demands and needs of any community hospital, and those of any practicing neuro- or vascular surgeon.

OSCAR S. DEPRIEST III, M.D.

Spontaneous Regression of Cancer. A Study and Abstract of Reports in the World Medical Literature and of Personal Communications Concerning Spontaneous Regression of Malignant Disease. TILDEN C. EVERSON, M.D., PH.D., F.A.C.S., AND WARREN H. COLE, M.D., F.A.C.S., F.R.C.S. (Eng., Hon.), F.R.C.S. (Edin., Hon.). Price, $20.00. Pp. 560, illustrated. Philadelphia: Saunders, 1966.

The authors have done a remarkable job in collecting some 176 cases of possible examples of spontaneous regression of cancer. The cases are, for the most part, well documented, including histologic confirmation of the malignancy by a group of noted pathologists. The majority of the reported instances of regression occurred in 4 types of cancer: adenocarcinoma of kidney (hypernephroma), neuroblastoma, malignant melanoma, and choriocarcinoma. Spontaneous regression of the common malignancies of breast, bowel, lung, and uterus was noted much less frequently. The possible causes of regression of the various types of cancer are discussed but no really new concepts are presented.

Because of the age of the material many of the photomicrographs and radiographs are indistinct and distorted and might have been better omitted with a subsequent decrease in the cost of publication.

The usefulness and appeal of this relatively expensive monograph are quite limited because it is essentially nothing more than a collation of appropriate case histories with little new information arising as a result. However, the accumulation of such cases in 1 volume

(*Continued on pages 60*)

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Precautions: As with all effective diuretics, vigorous therapy may produce electrolyte depletion. Patients with severely reduced renal function should be observed carefully since thiazides may be contraindicated. Care should be taken with patients predisposed to diabetes or gout. Patients with a tendency to potassium deficiency, as in hepatic cirrhosis or diarrheal syndromes, or those under therapy with digitalis, ACTH, or certain adrenal steroids, also should be watched carefully.

Side Effects: Nausea, flushing, constipation, skin rash, muscle cramps and gastric discomfort have occasionally been noted; rarely thrombocytopenia and bone marrow depression, photosensitivity, cholestatic jaundice, pancreatitis, perimacular edema, gout and diabetes have been caused by the administration of thiazides.

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Book Reviews

(*Continued from page 58*)

does remove some of the mystery from the quite unusual and scattered reports of spontaneous regression of cancer.

Richard L. Levin, M.D.

Emergency Care of the Sick and Injured. A Manual for Law-Enforcement Officers, Fire-Fighters, Ambulance Personnel, Rescue Squads and Nurses. By the Committee on Trauma, American College of Surgeons. Edited by Robert H. Kennedy, M.D., F.A.C.S. Price (paper), $2.00. Pp. 128, illustrated. Philadelphia: Saunders, 1966.

A word about the author and editor, Dr. Robert H. Kennedy, is appropriate. Dr. Kennedy was graduated from Amherst College and Columbia Medical School. He received his training in general surgery in the New York hospitals. He then devoted his entire life to traumatic surgery—teaching and preaching the care of the injured. He was one of the Founder Members of the Committee on Trauma of the American College of Surgeons when it was originally organized in 1921. To this Committee Dr. Kennedy has devoted a tremendous amount of his time and energies; when he thought it was time for him to retire from active surgical practice at the age of 67, he took on a full-time job for the Committee on Trauma as its Field Director.

His job was first to design, according to newer concepts, the Emergency Room in hospitals for both the urban and rural areas of the United States and to supervise the upgrading of the existing Emergency Rooms to meet the present-day demand. This meant not only construction and equipment but the proper training of personnel, both professional and adjunct, in the operations of the Emergency Room. To do this he traveled miles and miles, from city to city and from town to town, over this entire Nation in order to implement the program.

It became obvious to him and members of the Committee on Trauma that detailed instructions for the construction and equipment of Emergency Rooms were necessary. Such a book he edited and circulated to all the hospitals through the College of Surgeons and its regional representatives.

In this little book, "Emergency Care," which he has compiled, there are short concise chapters written on each subject by men of authority—doctors, police and ambulance personnel. To the physician the book may seem altogether too simple. On the other hand, it behooves every doctor to know everything in this book, regardless of his specialty. Since its publication, all physicians to whom I have spoken have acknowledged that this book did refresh their memory on the care of some particular injury at some point. For the recent medical school graduate, the book is invaluable. For the nurse, the ancillary personnel, and the ambulance driver and his personnel, it is mandatory knowledge.

As pointed out in the early chapters of his book, the same accident and the same injury will result in survival of the patient 10 times more frequently in the city than in the country. Our special job is to get this book to the ambulance attendants and the Emergency Room personnel of the small hospital and small community. Rescue squads have sprung up in every little village over the entire country as an opportunity for young men to get a thrill out of a roaring, speeding, noisy ambulance. At times these ambulance attendants do more harm to the individual at the scene of the accident and in his transportation to the hospital than would occur if some kind Samaritan passing down the road in his station wagon folded down his back seats and gently carried the patient recumbent to the hospital. The simple methods of care such as a patent airway and mouth-to-mouth resuscitation are impressed on the reader.

The book is easily and simply written. All words are understandable to anyone with an eighth grade education.

Dr. Kennedy is to be congratulated on doing the work and we physicians must in every way try to disseminate this knowledge to the people who need it most.

Milton C. Cobey, M.D.

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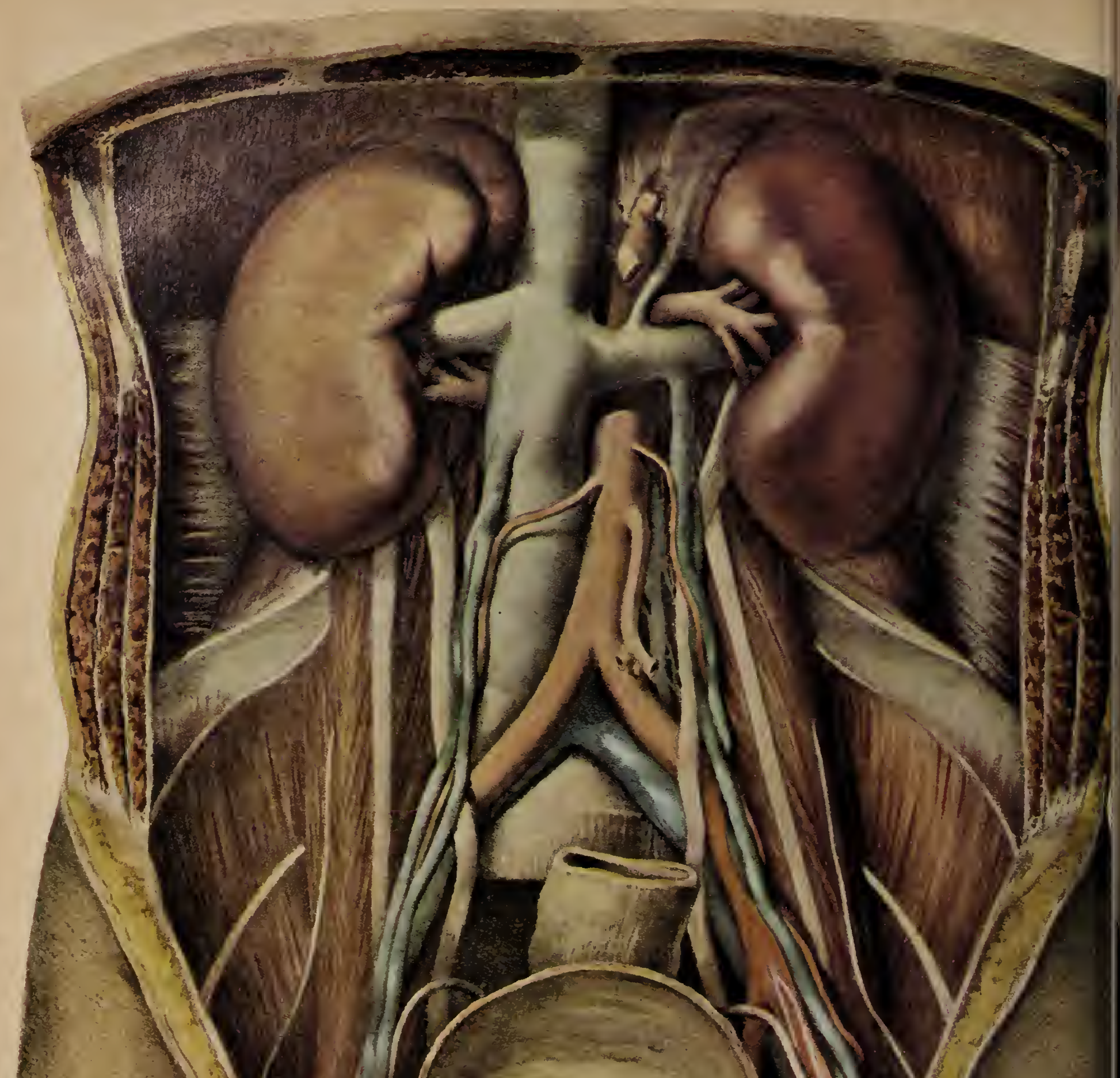

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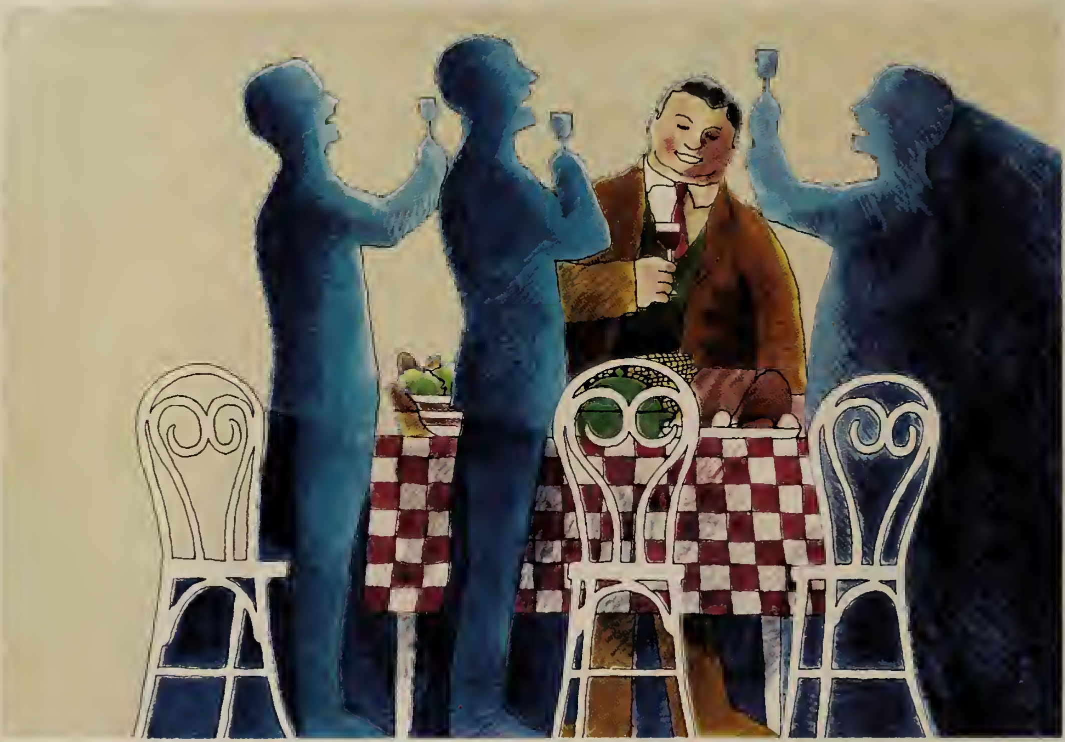

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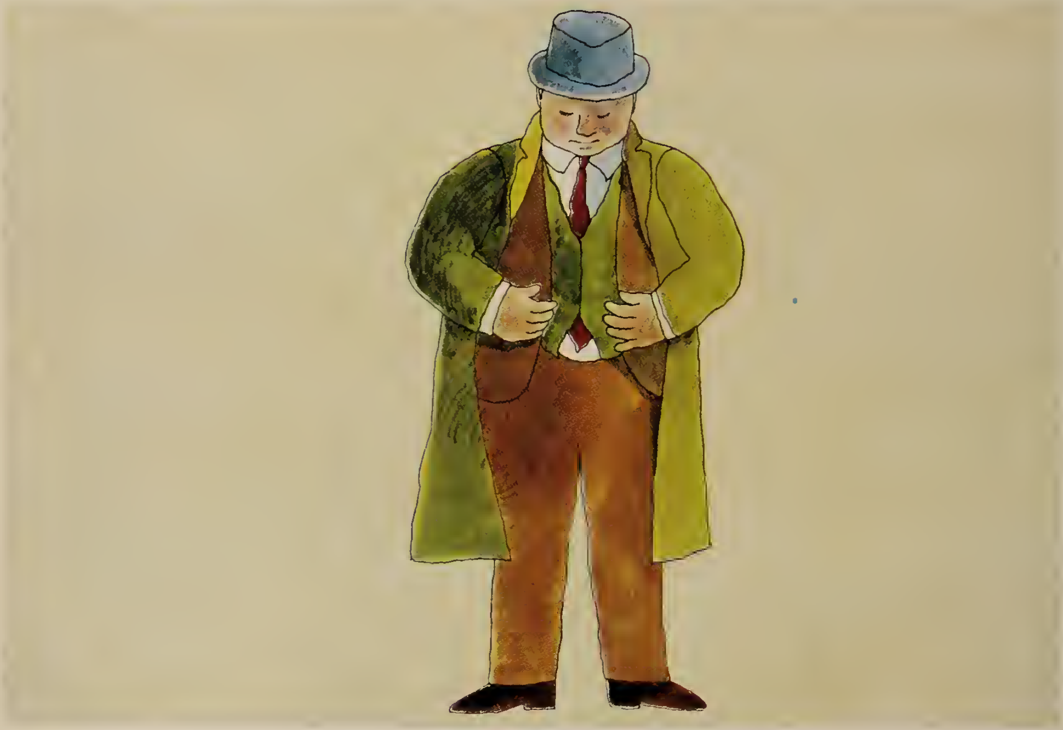

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Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

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Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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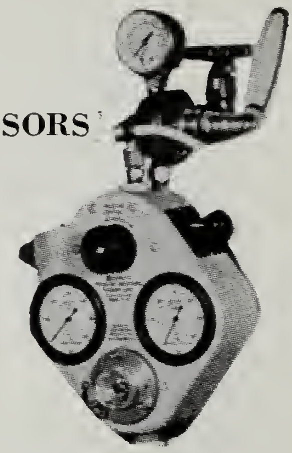

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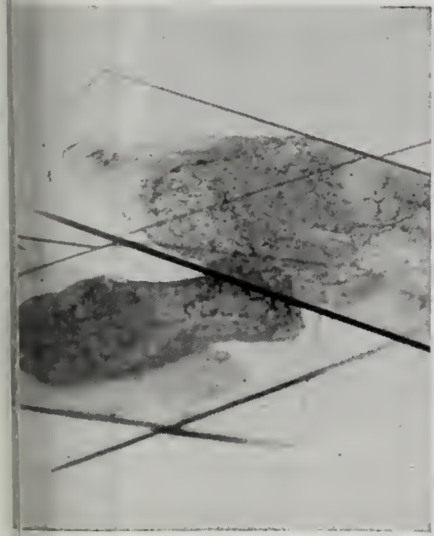

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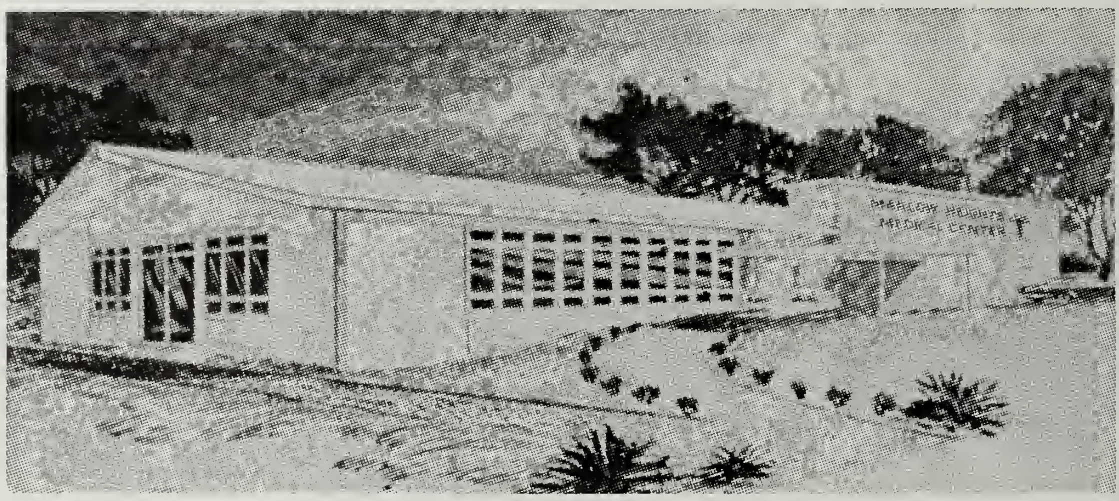

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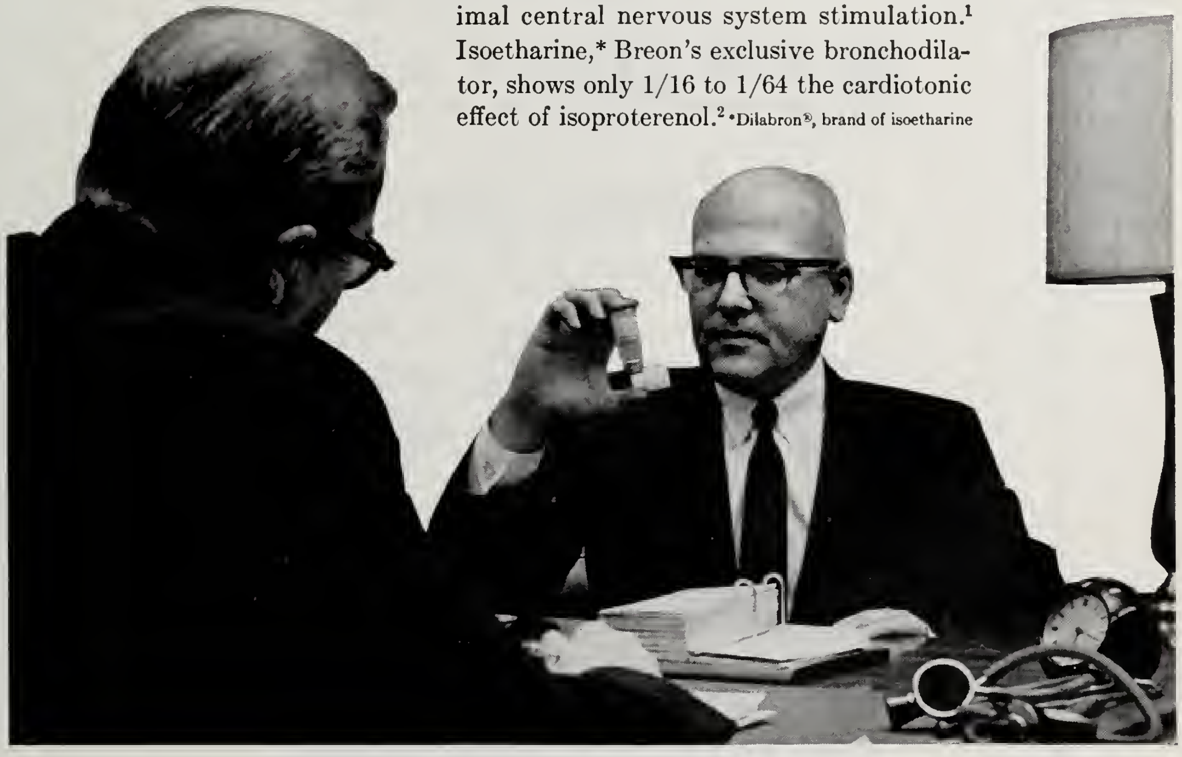

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SUPPLIED: 10 ml pressurized aerosol vials complete with measured dose valve and oral nebulizer.

References: 1. Spielman, A. D.: *Curr. Therap. Res.* 3:235 (June) 1961. 2. Herschfus, J. A.; Bresnick, E.; Levinson, L.; and Segal, M. S.: *Ann. Allergy* 9:769 (Nov.-Dec.) 1951.

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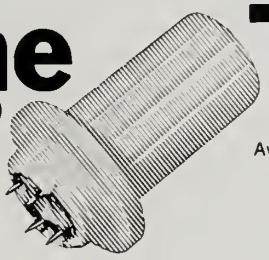

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Contraindications: Known sensitivity to erythromycin or sulfonamides. Because of the possibility of kernicterus with sulfonamides, do not use in pregnancy at term, premature or new born infants.

Warnings: As with other forms of sulfonamide therapy, carefully evaluate patients with liver or kidney damage, urinary obstruction, or blood dyscrasia. Deaths have been reported from hypersensitivity reactions and blood dyscrasias following use of sulfonamides. Perform blood counts and liver and kidney function tests if used repeatedly at close intervals or for long periods.

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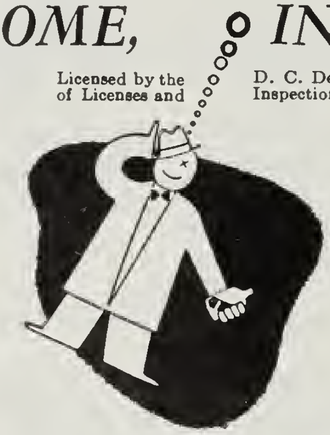

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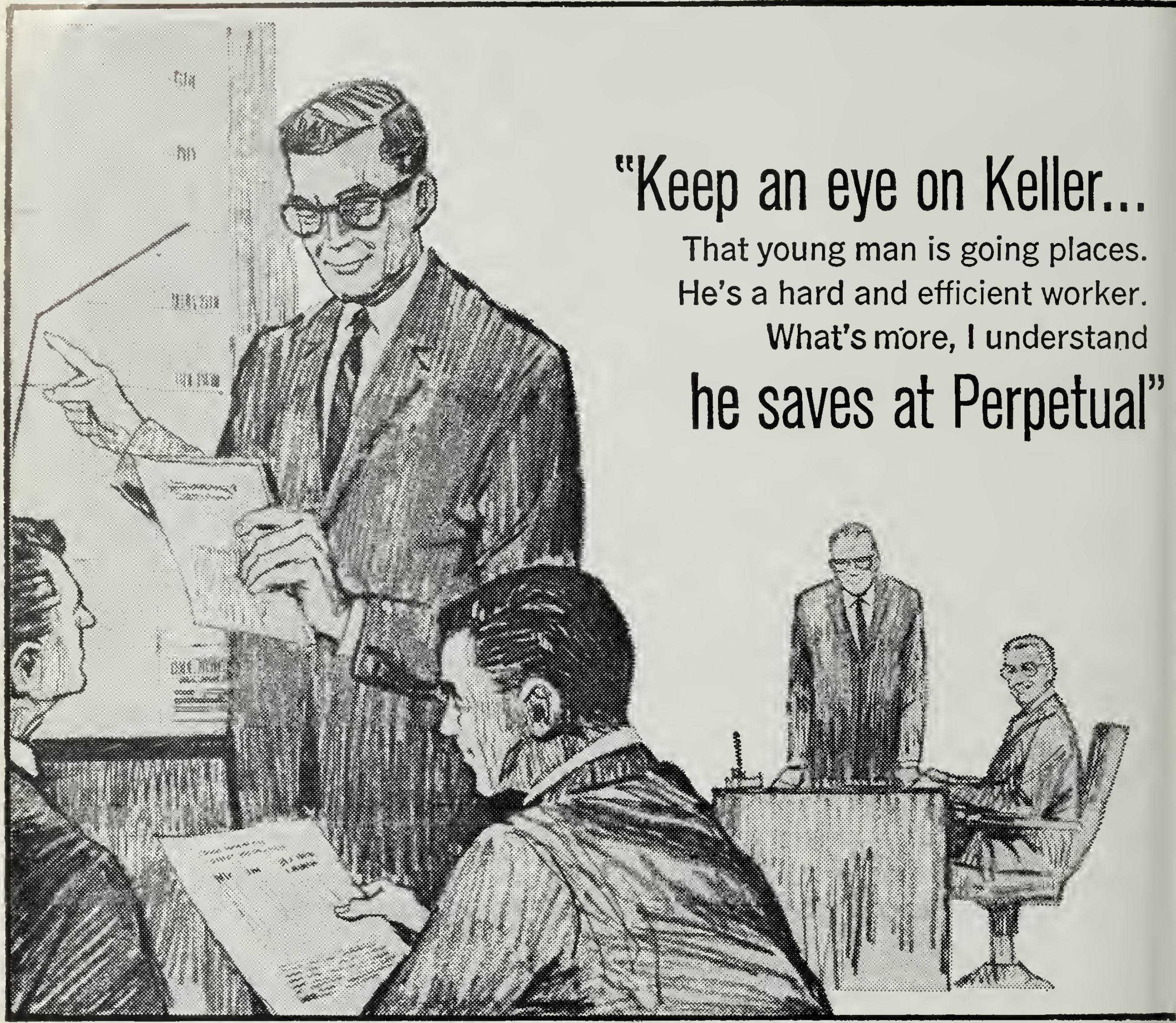

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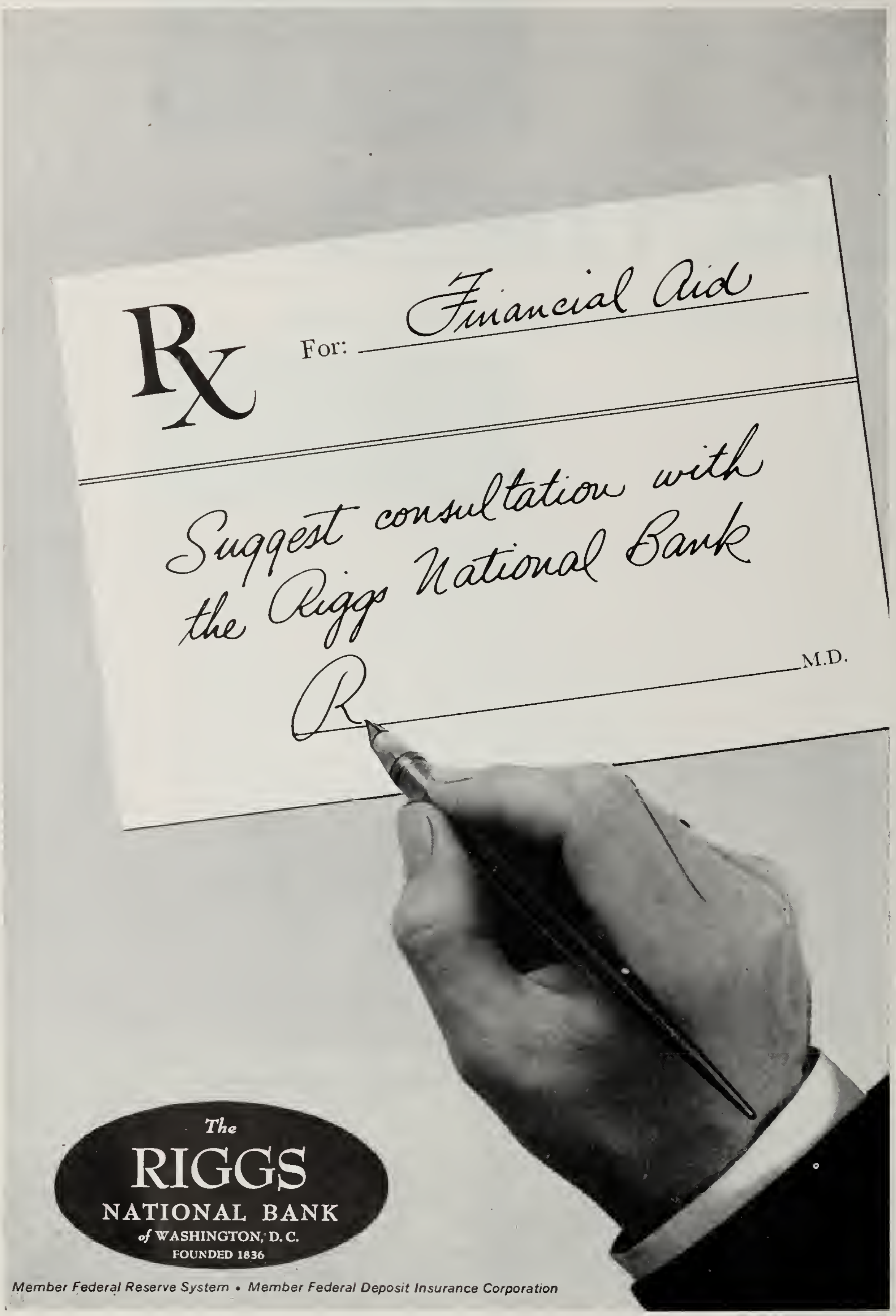
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The rationale: When combined, Erythrocin and the trisulfapyrimidines (triple sulfas) are indicated in infections that are more susceptible to the combination than to either agent alone. Such conditions are usually found in urinary, lower respiratory tract and chronic ear conditions.

The results: Clinical studies involving 142 young patients showed *an overall cure rate of 96.5%*. Side effects were experienced by only four of the patients.

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Chewable
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ERYTHROCIN®-SULFAS

Brief Summary

Indications: Use Erythrocin-Sulfas in infections more susceptible to the combination than to either agent alone. These are usually found in urinary, lower respiratory tract, and chronic ear infections.

Contraindications: Known sensitivity to erythromycin or sulfonamides. Because of the possibility of kernicterus with sulfonamides, do not use in pregnancy at term, premature or new born infants.

Warnings: As with other forms of sulfonamide therapy, carefully evaluate patients with liver or kidney damage, urinary obstruction, or blood dyscrasia. Deaths have been reported from hypersensitivity reactions and blood dyscrasias following use of sulfonamides. Perform blood counts and liver and kidney function tests if used repeatedly at close intervals or for long periods.

Precautions: Use sulfonamides with caution in patients with a history of allergy. Assure adequate fluid intake to prevent crystalluria and institute alkali therapy if indicated.

Adverse Reactions: Sulfonamide therapy may be associated with headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, injection of the conjunctiva and sclera, petechiae, purpura, hematuria and crystalluria.

Side effects due to erythromycin are infrequent, but occasional abdominal discomfort, nausea, or vomiting, urticaria and other skin rashes may occur.

If a reaction or overgrowth of nonsusceptible organisms occurs, withdraw the drug.

Supplied: The Granules for Oral Suspension come in bottles of 60 ml. and 150 ml. The Chewable tablets are in bottles of 50. Each 5-ml. teaspoonful of reconstituted Granules or each Chewable tablet provides erythromycin ethyl succinate equivalent to 125 mg. of erythromycin activity and 167 mg. each of sulfadiazine, sulfamerazine and sulfamethazine. 603303

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*Multiple of adult Minimum Daily Requirement supplied.
†The need for these substances in human nutrition has not been established.

Indications: 1. Functional fatigue such as that often associated with: a depressing life experience or stressful time of life; advancing years; convalescence; limited activity or confinement. 2. Poor appetite and vitamin-mineral deficiency as they occur in: patients having faulty eating habits; geriatric patients who are losing interest in food; patients convalescing from debilitating illness or surgery.

Dosage: Adults, 1 tablespoonful; children (over 15 years old), 1 to 2 teaspoonfuls; children (4 to 15 years old), 1 teaspoonful. To be taken three times daily 30 minutes before meals.

Contraindications: As with other drugs with CNS stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive compulsive states.

Side effects: Reports of overstimulation have been rare. Patients who are known to be unduly sensitive to the effects of stimulant drugs should be observed carefully in the initial stages of treatment.

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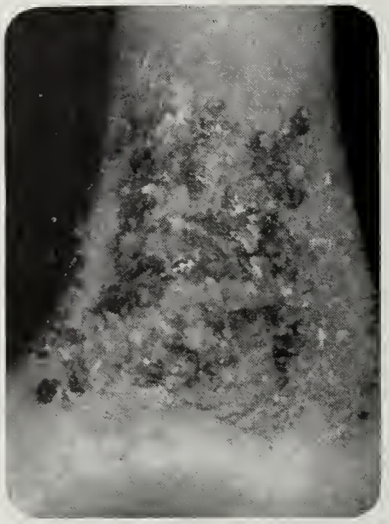
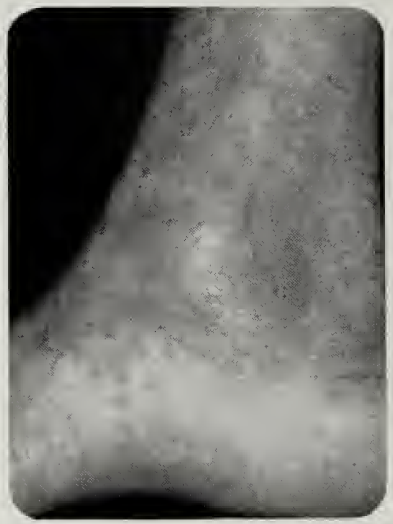


Before treatment



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Precautions and Side Effects: Do not use in the eyes or in the ear (if drum is perforated). A few individuals react unfavorably under certain conditions. If side effects are encountered, the drug should be discontinued and appropriate measures taken. Use on infected areas should be attended with caution and observation, bearing in mind the potential spreading of infection and the advisability of discontinuing therapy and/or initiating antibacterial measures. Generalized dermatological conditions may require systemic corticosteroid therapy. Steroid therapy, although responsible for remissions of dermatoses, especially of allergic origin cannot be expected to prevent recurrence. The use over extensive body areas, with or without occlusive nonpermeable dressings, may result in systemic absorption. Appropriate precautions should be taken. When occlusive nonpermeable dressings are used, miliaria, folliculitis and pyodermas will sometimes develop. Localized atrophy and striae have been reported with the use of steroids by the occlusive technique. When occlusive nonpermeable dressings are used, the physician should be aware of the hazards of suffocation and flammability. The safety of use on pregnant patients has not been firmly established. Thus, do not use in large amounts or for long periods of time on pregnant patients.

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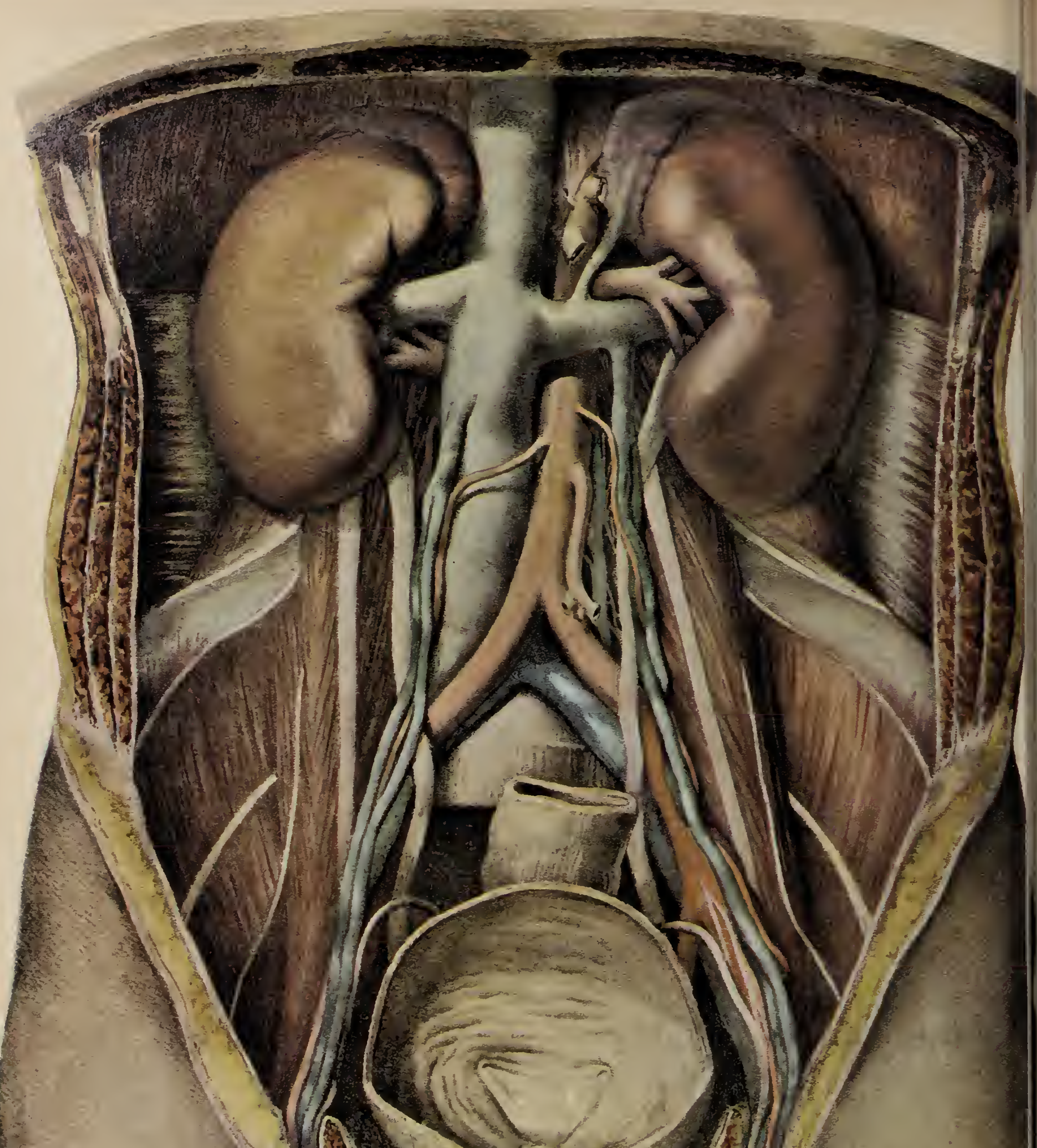

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Contraindications: Hypersensitivity to penicillin; infections due to penicillinase-producing staphylococci and other penicillinase-producing bacteria.

Precautions: If allergic reaction occurs, discontinue ampicillin and administer epinephrine, corticosteroids, antihistamines and/or pressor amines as indicated. Transient moderate elevation of SGOT values of undetermined significance was noted in a few infants. Liver and kidney function as well as hematopoietic tests are advisable during therapy, particularly in infants. As with other antibiotics, precautions should be taken against gastrointestinal superinfection. Safety for use in pregnancy has not been established.

Adverse Reactions: Occasional mild side effects as urticaria, skin rash, pruritus, diarrhea, nausea and vomiting. There have been no reports of blood dyscrasias, liver or kidney damage. Anaphylaxis has been reported.

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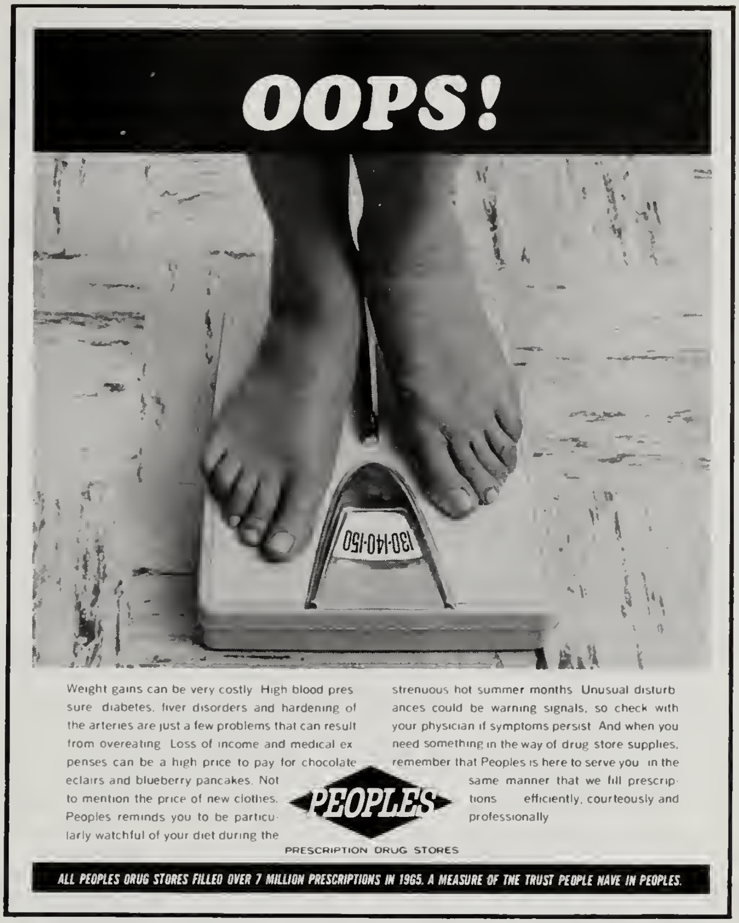

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The "Socio-geographic" mystery

Why is one man's gastric ulcer another man's duodenal?

Geographic variation in the *incidence* of peptic ulcer is a familiar fact. But the proclivity of certain *kinds* of ulcer for certain geographic areas is a recently recognized phenomenon.[1,2]

For example, in one particular Norwegian fishing village there is a tendency for patients to develop a gastric ulcer; anywhere else in Norway, ulcers are usually duodenal. Peruvians high in the Andes have more gastric ulcers than their compatriots in the lowlands. Why? Nobody knows.

Social variations, too. Even in the same geographic areas there are interesting variations. An Englishman's ulcer depends on his social standing—professional men suffer with duodenal ulcers, while workingmen have more of the gastric variety. In southern India the pattern is reversed. Here, duodenal ulcers are common among laborers and agricultural workers and rare among the upper classes.

Investigators are exploring every possible theoretical avenue in their search for the cause of peptic ulcer. Of all the factors implicated in ulcerogenesis, the one that is generally acknowledged to be of primary importance is hypersecretion of gastric acid.[3-8] Or, as one author states it: "The medical management of peptic ulcer pharmacologically is, in the final analysis, concerned largely with the effective inhibition of peptic activity."[3]

Robinul (glycopyrrolate) provides potent, rapid, specific antisecretory action confirmed by gastric analyses and x-ray evidence of clinical effectiveness.[3,7,9-12] Relieves pain with "impressive" promptness.[8] Quickly alleviates acute discomfort, and effectively counteracts gnawing pain, preprandial midepigastric pain, belching and other ulcer symptoms.[7] Suppression of nocturnal pain is "outstanding."[13] Maximally effective doses may be given with minimal side reactions, and the incidence of unwanted anticholinergic effects is negligible.[3,7-14]

no matter what the ulcer theory...the fact is that

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(brief summary follows)

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Indications: In addition to its primary indications for duodenal and gastric ulcer, Robinul (glycopyrrolate) is indicated for other GI conditions that may benefit from anticholinergic therapy. Robinul-PH Forte (glycopyrrolate 2 mg. with phenobarbital) is indicated when these situations are complicated by mild anxiety and tension.
Contraindications: Glaucoma, urinary bladder neck obstruction, pyloric obstruction, stenosis with significant gastric retention, prostatic hypertrophy, duodenal obstruction, cardiospasm (megaesophagus), and achalasia of the esophagus, and in the case of Robinul-PH Forte, sensitivity to phenobarbital.
Precautions: Administer with caution in the presence of incipient glaucoma.
Adverse Reactions: Dryness of the mouth, blurred vision, urinary difficulties, and constipation are rarely troublesome and may generally be controlled by reduction of dosage. Other side effects associated with the use of anticholinergic drugs include tachycardia, palpitation, dilatation of the pupil, increased ocular tension, weakness, nausea, vomiting, headache, dizziness, drowsiness, and rash.
Dosage: Dosage should be adjusted according to individual patient response. Average and maximum recommended dose is 1 tablet 3 times a day: in the a.m., early p.m., and at bedtime. *See product literature for full prescribing information.*
Supply: Robinul (glycopyrrolate 1 mg.); Robinul Forte (glycopyrrolate 2 mg.); Robinul-PH (glycopyrrolate 1 mg.) with phenobarbital 16.2 mg. (Warning: May be habit-forming); Robinul-PH Forte (glycopyrrolate 2 mg.) with phenobarbital 16.2 mg. (Warning: May be habit-forming.) In bottles of 100 and 500 scored tablets.
References: 1. Jones, F. A., and Gummer, J. W. P.: Clinical gastroenterology, Springfield, Ill., Charles C Thomas, 1960, pp. 322-3. **2.** Bockus, H. L.: Gastroenterology, 2nd ed., vol. I, Philadelphia, Saunders, 1963, p. 468. **3.** Sun, D. C. H.: Ann NY Acad Sci 99:153 (Feb. 28) 1962. **4.** Moore, V. A.: Postgrad Med 38:216 (Sept.) 1965. **5.** Dragstedt, L. R., Woodward, E. R., Storer, E. H., Oberhelman, H. A., Jr., and Smith, C. A.: Ann Surg 132:626 (Oct.) 1950. **6.** Posey, E. L., Jr., Smith, P., Turner, C., and Aldridge, J.: Amer J Dig Dis 10:399 (May) 1965. **7.** Lamphier, T. A., Siegel, L., and Goldberg, R. I.: Amer J Gastroent 37:551 (May) 1962. **8.** Kasich, A. M., and Fein, H. D.: Ibid 39:61 (Jan.) 1963. **9.** Epstein, J. H.: Ibid 37:295 (Mar.) 1962. **10.** Moeller, H. C.: Ann NY Acad Sci 99:158 (Feb. 28) 1962. **11.** Slanger, A.: J New Drugs 2:215 (Jul.-Aug.) 1962. **12.** Barman, M. L., and Larson, R. K.: Amer J Med Sci 246:325 (Sept.) 1963. **13.** Shutkin, M. W.: Amer J Gastroent 38:682 (Dec.) 1962. **14.** Fleshler, B.: J New Drugs 2:211 (Jul.-Aug.) 1962.

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BOOKS RECEIVED

Acknowledgment is made of the following books which have recently been received.

Current Practice in Orthopaedic Surgery 1966, Volume 3. Edited by JOHN P. ADAMS, B.S., M.D., F.A.C.S. Price, $18.75. Pp. 276, illustrated. St. Louis: Mosby, 1966.

Primer on Prematurity and High-risk Pregnancy. S. GORHAM BABSON, M.D., AND RALPH C. BENSON, M.D. Price, $10.50. Pp. 194, illustrated. St. Louis: Mosby, 1966.

Clinical Management of Behavior Disorders in Children, 3rd ed. HARRY BAKWIN, M.D., AND RUTH MORRIS BAKWIN, M.D. Price, $14.50. Pp. 652, illustrated. Philadelphia: Saunders, 1966.

Surgical Diseases of the Chest, 2nd ed. Edited by BRIAN BLADES, M.D. Twenty contributors. Price, $25.00. Pp. 687, with 295 illustrations. St. Louis: Mosby, 1966.

Stereoscopic Atlas of Mastoidotympanoplastic Surgery. HAROLD F. SCHUKNECHT, M.D., WERNER D. CHASIN, M.D., AND JOHN M. KURKJIAN, M.D. Price, $26.50. Pp. 92, with 51 figures and 70 stereoscopic views in full color on 10 View-Master® reels keyed to labeled drawings and figures, and a View-Master® compact viewer. St. Louis: Mosby, 1966.

Synopsis of Gross Anatomy. JOHN B. CHRISTENSEN, PH.D., AND IRA ROCKWOOD TELFORD, PH.D. Price, $5.95. Pp. 248, with 81 illustrations. New York: Harper & Row (Hoeber Medical Division), 1966.

The Consumers Union Report on Family Planning, 2nd ed. Prepared by the Editors of Consumer Reports and the following consultants: ALAN F. GUTTMACHER, M.D., AQUILES J. SOBRERO, M.D., AND RAEL JEAN ISAAC. Price (paper), $1.75. Pp. 191, illustrated. Mt. Vernon, N.Y.: Consumers Union of U.S., 1966.

Conflict in Society. A Ciba Foundation Symposium. Edited by ANTHONY DE REUCK, M.Sc., D.I.C., A.R.C.S., AND JULIE KNIGHT, B.A. Price, $13.00. Pp. 467. Boston: Little, 1966.

Synopsis of Dermatology. WILLIAM D. STEWART, M.D., F.R.C.P.(C), JULIUS L. DANTO, M.D., AND STUART MADDIN, M.D. Price, $10.85. Pp. 664, with 155 figures and 32 color plates. St. Louis: Mosby, 1966.

Sudden Death in Infants. Proceedings of the Conference on Causes of Sudden Death in Infants, September 1963, Seattle, Washington. Edited by RALPH J. WEDGWOOD, M.D., AND EARL P. BENDITT, M.D.; WANDA M. BURNETT, Technical Editor. PHS Publication No. 1412. Price (paper), $1.75. Pp. 165, illustrated. Washington, D. C. 20402: Superintendent of Documents, U. S. Government Printing Office, 1966.

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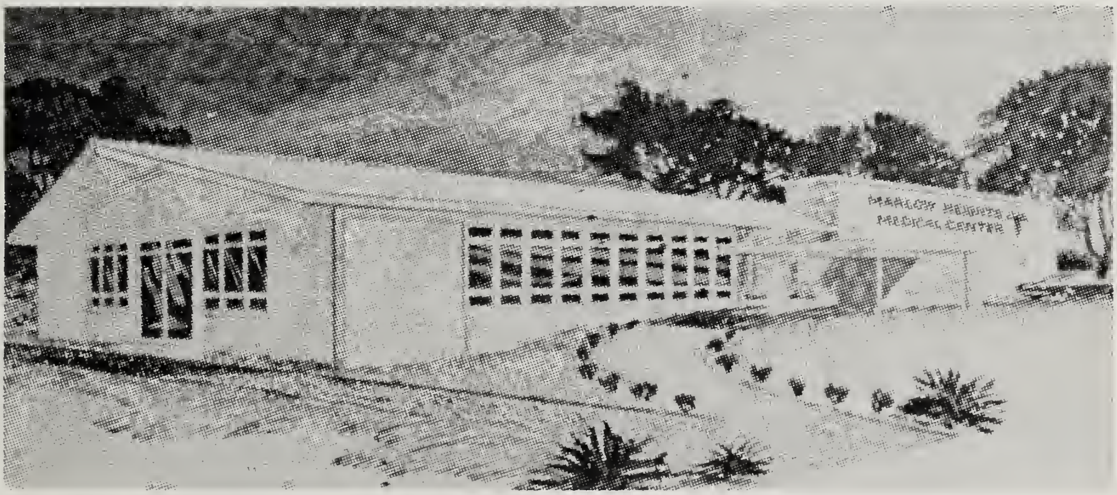

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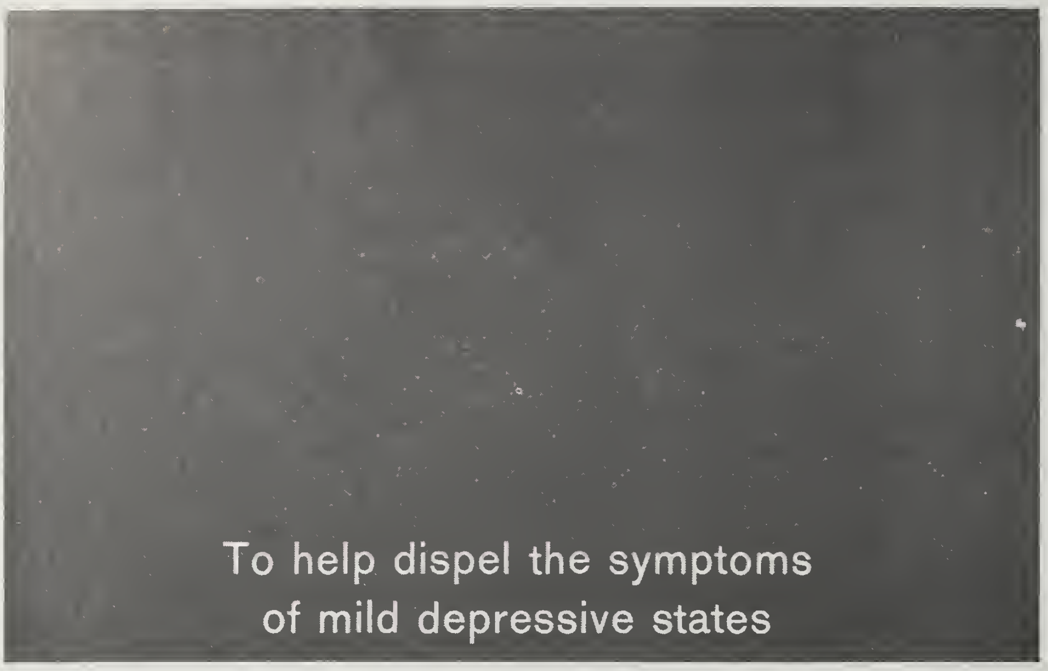

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- **in CONSTIPATION** . . . Konsyl and L. A. Formula retain water in the stool against the strong dehydrating function of the colon.
- Since a liquid stool contains only 10 per cent more water than the hardest scybalum*

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PLANTAGO OVATA COATING
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For the obese patient who needs calorie free medication

L.A.FORMULA

For the finicky eater who requires unsurpassed palatability

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the bowel normalizers of choice

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**Tainter, M.L. and Buchanan, O.H., Ann. N.Y. Acad. Sc. 54:438, 1954*

This tiny amount
of active ingredient
provides
secure
protection
against
pregnancy

Massive, worldwide clinical experience

Weight gain as infrequent as weight loss

New freedom from undesirable effects

New low cost

Contraindications—Mammary or genital carcinoma should be ruled out prior to administering Ovulen. Undiagnosed vaginal bleeding is also a contraindication to Ovulen use. A history of thrombophlebitis or pulmonary embolism, or both, is a contraindication to the use of Ovulen, unless its use is judged by the physician to be necessary despite the possible risk. Ovulen should not be used in women with suspected or overt liver dysfunction or disease. Ovulen is contraindicated in pregnant and nursing women and in patients with a history of cerebrovascular accident.

Warnings—Medication should be discontinued pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. Medication should be withdrawn if examination reveals papilledema or retinovascular lesions. Since the safety of Ovulen therapy in pregnancy has not yet been established, it is recommended that, in a patient who has missed two consecutive menstrual periods, pregnancy be ruled out before oral contraceptive therapy is continued.

Precautions—Because Ovulen may aggravate a tendency toward fluid retention in some patients, it should be administered cautiously to patients with a history of renal or cardiovascular disease (including hypertension), asthma, epilepsy or migraine. Any possible influence of long-term Ovulen therapy on pituitary, adrenal cortical, ovarian, hepatic or uterine functions requires further study. Oral contraceptives also should be administered cautiously to diabetic patients since a decrease in glucose tolerance has been observed in some patients taking these drugs. Patients on Ovulen may occasionally show abnormal glucose tolerance tests, but this does not necessarily indicate the presence of diabetes. Significant increases in platelet count, prothrombin and proconvertin tests, plasma thrombotic activity and plasma proteolytic activity have been reported.

Since estrogens may affect results of serum protein bound iodine and other thyroid function tests, these tests should not be considered definitive until Ovulen therapy has been discontinued for at least sixty days. Adrenal steroid serum levels and excretion may be affected by estrogens; the Metopirone® (SU-4885) test of pituitary-adrenal function may also be depressed. Abnormalities in hepatic function tests have also been reported, including some interference with dye excretion by the liver. This interference may give rise to Bromsulphalein® retention and jaundice in susceptible individuals. Serious liver dysfunction should be ruled out before continuing Ovulen administration when abnormalities in liver function tests occur.

Patients with a history of psychic depression should be observed carefully during treatment with oral contraceptives, and such treatment should be discontinued if depression recurs to a serious degree. Pre-existing fibroids may increase in size during Ovulen therapy. Such fibroids may regress to pretreatment size after Ovulen is stopped. In the event of breakthrough bleeding the possibility of nonfunctional causes should be borne in mind. Additional means of contraception should be used during the first seven days of Ovulen administration in the first treated cycle, because early ovulation may possibly occur.

Side Actions—The following adverse reactions have been reported with Ovulen; however, a causal relationship to Ovulen administration has not been established in all of the listed complaints: headache, dizziness, depression, breast complaints, amenorrhea, chloasma, vomiting, allergy, edema, migraine, pulmonary embolism, thrombophlebitis, visual difficulties, nervousness, rash, itching, decrease in libido, tiredness, malaise, hair loss and hair growth. A small incidence of nausea, spotting and breakthrough bleeding has been reported; these complaints tend to diminish markedly or disappear after the first cycle of treatment. Some of these side actions have required discontinuance of the drug.

Dosage—One tablet daily for 20 consecutive days beginning 5 days after the onset of menstruation.

Before prescribing see Detailed Product Information, Ovulen.

An extensive list of references on Ovulen is included in the literature mailed to physicians.

Research in the Service of Medicine
G. D. SEARLE & CO.
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1mg.

Each tablet contains:
ethynodiol diacetate 1 mg
mestranol 0.1 mg.

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is effective b.i.d.

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300 mg Tablet
mid-morning
hours
between
doses
one
300 mg Tablet
mid-evening

It's made for b.i.d.

Effective in a wide range of everyday infections—respiratory, urinary tract and others—in the young and aged—the acutely or chronically ill—when the offending organisms are tetracycline-sensitive.

Contraindication—History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive systemic accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort.

Precautions and Side Effects—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. Use of demethylchlortetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long-term use but has also been observed in short treatment courses. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment. Side reactions include glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and dermatitis. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Anaphylactoid reactions have been reported.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products.

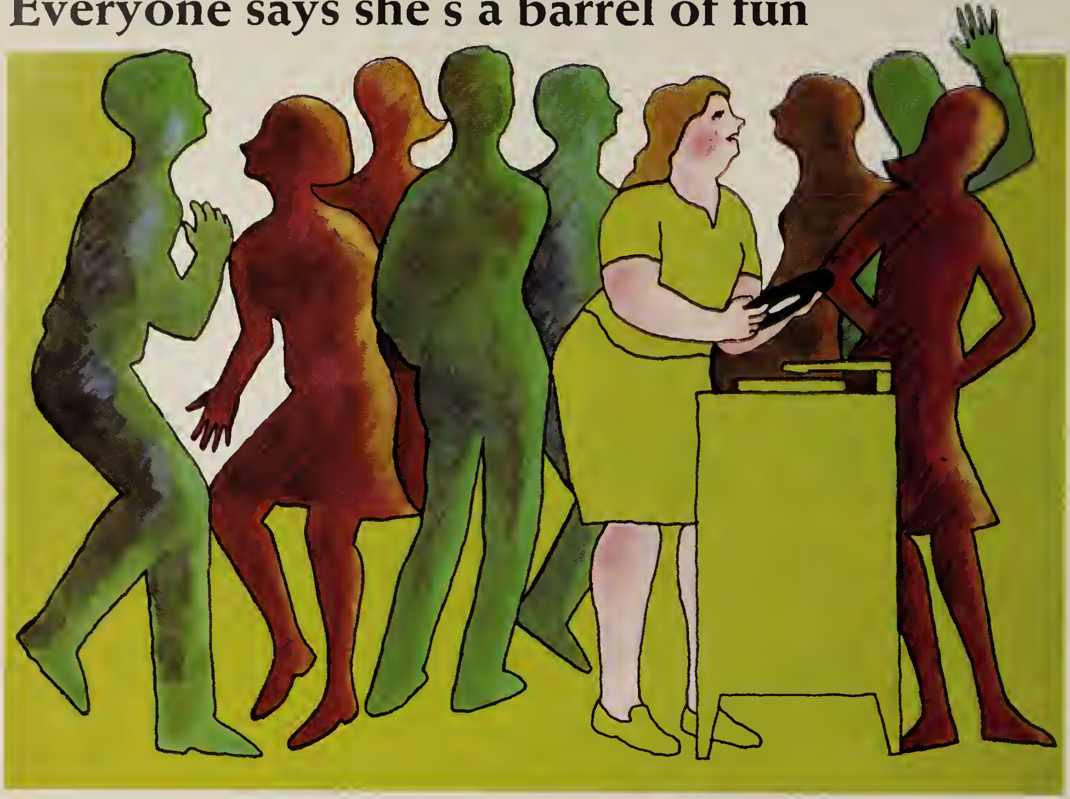
Capsules: 150 mg; *Tablets:* film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York

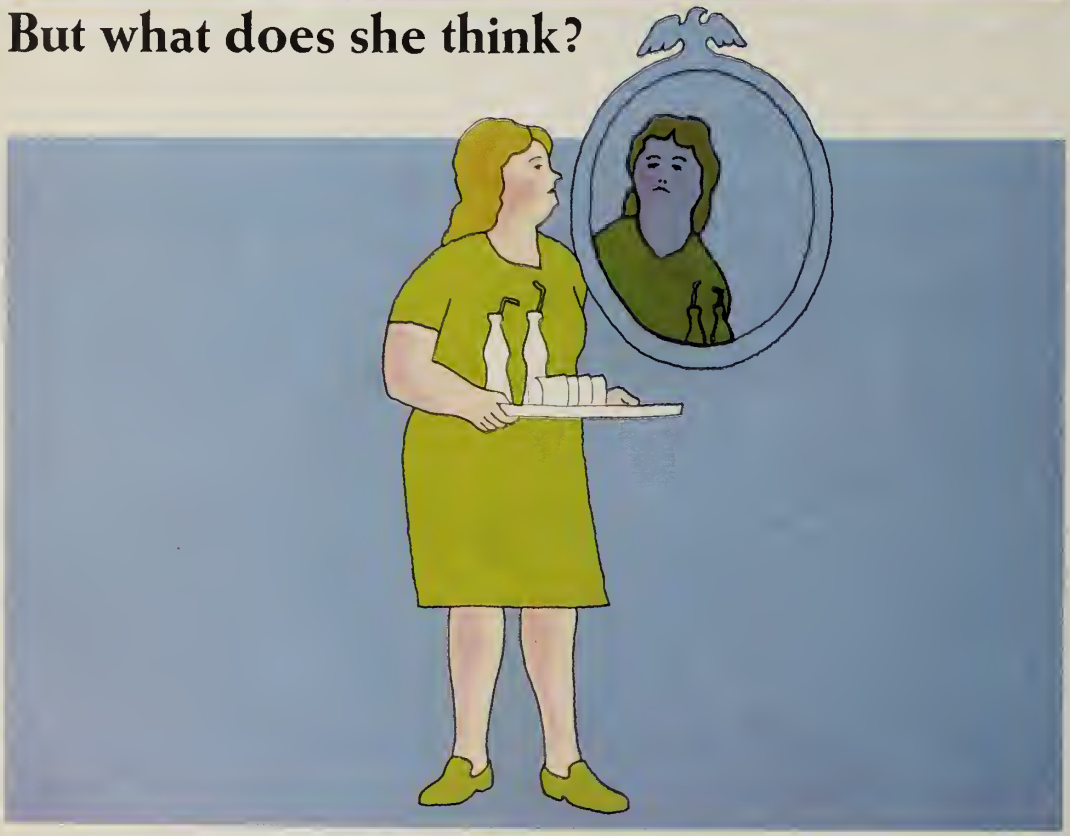
Lederle

417-6—4076

Everyone says she's a barrel of fun



But what does she think?



Many overweight patients can benefit from the appetite control provided by the sustained anorexigenic-tranquilizing action of BAMADEX SEQUELS: anorexigenic action of amphetamine; tranquilizing action of meprobamate; prolonged action through sustained release of active ingredients.

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DEXTRO-AMPHETAMINE SULFATE (15 mg.) WITH MEPROBAMATE (300 mg.) SUSTAINED RELEASE CAPSULES

to help establish a new dietary pattern

Contraindications: Dextro-amphetamine sulfate: in hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions to meprobamate.

Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness.

Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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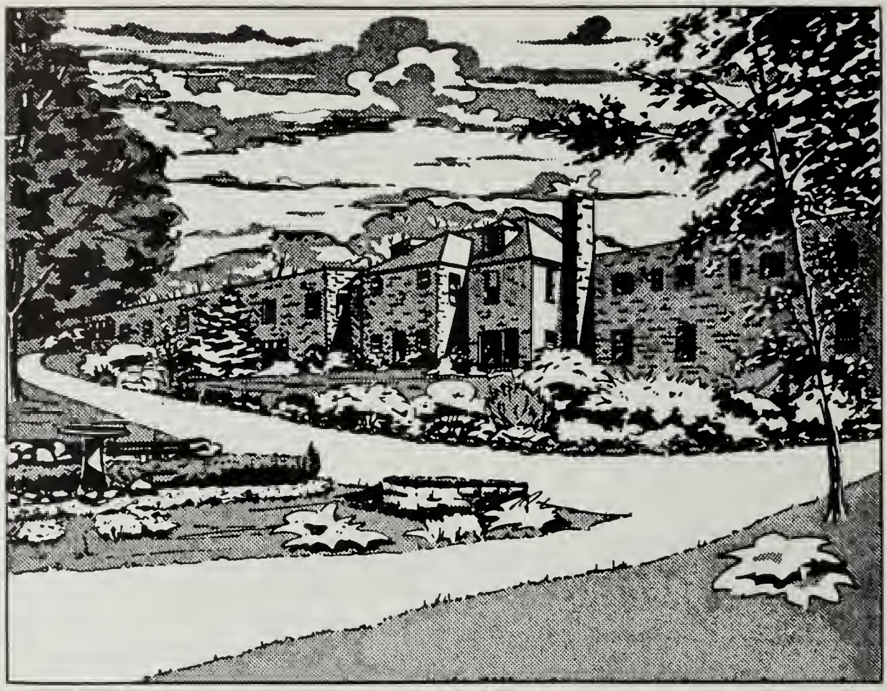

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low-cost tetracycline/antifungal therapy

for broad-spectrum activity
plus specific antifungal prophylaxis
at significant patient savings

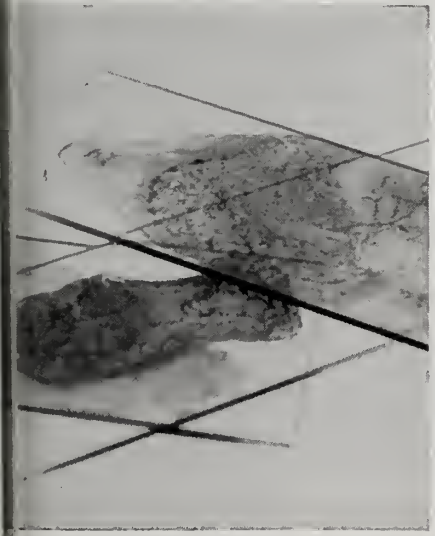
Whenever tetracycline is indicated in these candidates for Candida:

diabetic patients

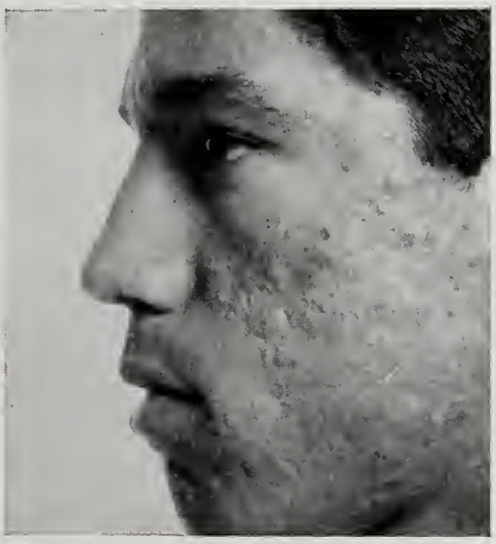
2. nonpregnant women with a history of recent or recurrent monilial vaginitis

3. elderly or debilitated patients

patients with a past history of moniliasis



5. patients on long-term tetracycline or corticosteroid therapy



BRISTOL THERAPEUTIC SUMMARY: For complete information consult Official Package Circular. *Indications:* Infections of respiratory, gastrointestinal and genitourinary tracts and skin and soft tissues due to tetracycline-sensitive organisms, in patients with increased susceptibility to monilial infections. *Contraindications:* The drug is contraindicated in patients hypersensitive to its components. *Warnings:* Photodynamic reactions have been produced by tetracyclines. Natural and artificial sunlight should be avoided during therapy. Stop treatment if skin discomfort occurs. With renal impairment, systemic accumulation and hepatotoxicity may occur. In this situation, lower doses should be used. Tooth staining and enamel hypoplasia may be induced during tooth development (last trimester of pregnancy, neonatal period and childhood). *Precautions:* Bacterial superinfection may occur. Infants may develop increased intracranial pressure with bulging fontanels. In gonorrheal therapy, serologic tests for syphilis should be conducted initially and monthly for 3 months. *Adverse Reactions:* Glossitis, stomatitis, nausea, diarrhea, flatulence, proctitis, vaginitis, dermatitis, and allergic reactions may occur. *Usual Adult Dosage:* 1 capsule *q.i.d.* Continue therapy for 10 days in beta-hemolytic streptococcal infections. Administer one hour before or 2 hours after meals. *Supply:* Capsules, bottles of 16. Each capsule contains tetracycline phosphate complex equivalent to 250 mg. tetracycline HCl activity and 250,000 units of nystatin.

BRISTOL

BRISTOL LABORATORIES
Division of Bristol-Myers Company
Syracuse, New York

Tetrex-F®

ach capsule contains tetracycline phosphate complex equivalent to tetracycline hydrochloride 250 mg. and nystatin 250,000 units.

Tetrex-F is priced lower
than most
tetracycline-antifungal products.

Vistaril

(HYDROXYZINE)

tranquilizes without addiction or drug dependency

Clinical Experience

In its eight-year record of experience in which over one billion doses have been prescribed, there is no evidence of addiction to hydroxyzine.

Clinical Background

In over 500 published studies involving 15,000 individual cases, neither dependency nor addiction has been reported with hydroxyzine.

Since 1849

Pfizer

Science for the world's well-being®

Even in the anxious, dependent, psychoneurotic...

Four hundred and fifty patients, most of them classified as functional neurotics, were treated with hydroxyzine for periods of five months to four and one-half years. Sustained good-to-excellent relief from symptoms of anxiety and tension was attained in 401 (89%) of the series. *"Cumulative effects, habituation or addiction to hydroxyzine was not noted during the entire period of this study."*

Shalowitz, M.: Int. Rec. Med. 174:357, June, 1961.

Even in the classically dependent alcoholic...

Vistaril (hydroxyzine) was evaluated for relief of postalcoholic syndrome in 52 chronic alcoholic outpatients over a period of two to four weeks. Many patients received partial to complete relief of psychomotor agitation, anxiety, irritability, craving, insomnia, depression, anorexia, nausea and tension. *"No evidence of toxicity or habituation was noted." "No difficulty was experienced in discontinuing medication."*

Greenhouse, H. R.: Med. Times 91:1069, November, 1963.

Of 326 alcoholics treated with hydroxyzine for the postalcoholic syndrome, satisfactory control was achieved in 276 (85%). *"As is not the case with other ranquilizers, hydroxyzine has no published record of causing addiction and dependence or withdrawal symptoms."* Goldman, H. I.: Southwest. Med. 42:276, June, 1961.

Even in the institutionalized patient needing long-term treatment...

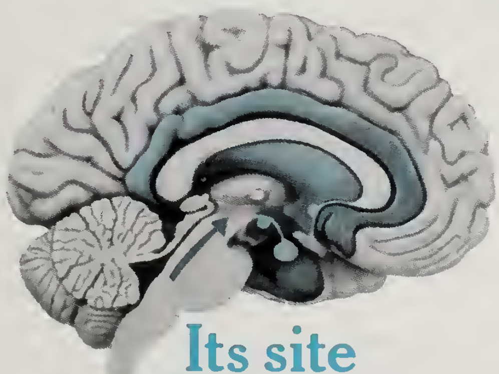
One hundred and fifty-two institutionalized emale patients were studied on long-term, high-dose therapy.

Even at high dosages, hydroxyzine *. . . did not produce either euphoria or depression."*

apolla, A.: Clin. Med. 8:1332, July, 1961.

No other tranquilizer is as precise, as uncomplicated as Vistaril®

(HYDROXYZINE)



Its site of action is the seat of anxiety

turn page for brief summary...

BRIEF SUMMARY

Contraindications: Hypersensitivity to hydroxyzine. The parenteral solution, for intramuscular or intravenous use, *must not* be injected subcutaneously or intra-arterially.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available, to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants. In conjunctive use, dosage for these drugs should be decreased, as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. On reported intravenous injection a few instances of digital gangrene have occurred distal to the injection site, considered to be due to inadvertent intra-arterial injection or possibly periarterial extravasation. Therefore, particular caution should be observed to insure injection only into intact veins; avoid either intra-arterial injection or extravasation. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity has been reported in some hospitalized patients given higher than recommended dosage.

When this product is given intravenously undiluted, minimal amounts of intravascular hemolysis occur at the site of injection. Giving the maximum recommended intravenous dose (100 mg.) to adults results in immediate transient hemolysis with the liberation of a total of 2-3 grams of hemoglobin, which, in some individuals, can cause small amounts of hemoglobinuria. This compares with the normal red cell destruction from which approximately 8 Gm. of hemoglobin are liberated every 24 hours. If the hydroxyzine is diluted with 50 cc. of normal saline and given during a period of four minutes or more, this phenomenon does not occur.

Supply: Vistaril (hydroxyzine pamoate) Capsules: Equivalent to 25 mg., 50 mg., 100 mg. hydroxyzine HCl. Vistaril (hydroxyzine pamoate) Oral Suspension: Equivalent to 25 mg. hydroxyzine HCl per 5 cc. teaspoonful. Vistaril (hydroxyzine HCl) Parenteral Solution: 25 mg./cc.—10 cc. vial and 50 mg./cc.—2 cc. and 10 cc. vial; Isoject,® 25 and 50 mg. per cc., 1 cc. per unit.

More detailed professional information available on request.

The Vistaril site of action is the seat of anxiety

Pfizer *Science for the world's well-being®*
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SQUIBB NOTES ON THERAPY

Breast-feeding and the "modern mother"

Despite a mild resurgence of interest in the importance of breast-feeding a few years ago, many women today do not choose to nurse their young. This is for a variety of reasons—social, economic, cultural and sometimes medical. In such cases the physician's task is to find the most suitable means of preventing lactation and easing the pain of breast engorgement.

The means of therapy

The value of hormone therapy for this indication is of course well established. Both androgen and estrogen are known to inhibit the production and secretion of the lactogenic hormone by the anterior pituitary. As estrogen levels decline sharply at parturition, lactogenesis is established. When androgen and estrogen are administered to the patient before the release of the lactogenic hormone lactation and breast engorgement are usually prevented.

The time of therapy

The time of administration of this combined medication is crucial; it must be given early enough to suppress the pituitary prolactin and last long enough to permit physiologic readjustment during the puerperium. Excellent results are most often seen when therapy is administered before the onset of the second stage of labor.

However, factors other than effectiveness must also be considered. The agent selected should not interfere in any way with parturition, subsequent uterine involution and the restoration of normal ovarian cyclic function. Furthermore, it should not cause rebound breast engorgement or other manifestations of hormonal imbalance.

A balanced formulation

Providing single-dose therapy for the prevention of lactation and breast engorgement, Deladumone OB is a potent androgen-estrogen combination with a prolonged action. The optimal balance of androgenic and estrogenic hormones achieved in this preparation minimizes the disadvantages inherent in single hormone therapy, such as rebound breast engorgement. Involution of the uterus and resumption of menstrual cycles are not affected.

As reported in a recent published study (Roser, D. M.: Obstet. & Gynec. *27*:73, 1966), Deladumone OB provided good suppression of breast engorgement in 95.3% and suppression of lactation in 81.1% of 86 obstetrical patients. These results are in general agreement with those of many earlier investigations; in several studies this injectable androgen-estrogen combination proved to be superior to oral medication.

Dosage:

As a single injection of 2 cc. before the onset of the second stage of labor.

Contraindications:

Established or suspected mammary cancer or genital malignancy.

Precautions and Side Effects:

Certain patients may be unusually responsive to either estrogenic or androgenic therapy. In such individuals virilization, uterine bleeding or mastodynia may occur.

Supply:

Deladumone OB, providing 180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc., is available in 2 cc. Unimatic® disposable syringes and in 2 cc. vials. Both preparations are dissolved in sesame oil, with 2% benzyl alcohol as a preservative. *Before use, consult product literature for full prescribing information.*

Deladumone® OB

Squibb Testosterone Enanthate (180 mg./cc.)
and Estradiol Valerate (8 mg./cc.)
Single-dose injection for lactation inhibition

SQUIBB *'The Priceless Ingredient' of every product is the honor and integrity of its maker.*

with so many other thyroid hormones to choose from...

why Synthroid®?

sodium levothyroxine, FLINT

Animal gland products are still widely used today. SYNTHROID (sodium levothyroxine), however, offers important advantages in the treatment of thyroid deficiency and related conditions.

CHECK OUR REASONS AND YOU'LL AGREE:

full therapeutic value

SYNTHROID (sodium levothyroxine) is 100% pure thyroid hormone . . . a drug of definite and uniform composition. Each batch is assayed by chemical and physical measurement . . . a more accurate method than biologic standardization. SYNTHROID (sodium levothyroxine) does *not* deteriorate in storage or in high humidity conditions. Your patients consistently receive the dosage you prescribe.

it is competitively priced

Patient costs are competitive with animal gland products. In comparison to the other form of synthetic thyroid hormone, SYNTHROID (sodium levothyroxine) costs approximately half as much.

smooth response

With SYNTHROID (sodium levothyroxine), there is little possibility of a metabolic surge that can compromise cardiac function. SYNTHROID (sodium levothyroxine), after absorption and protein binding, is released at a *physiologic* rate. *This assures a smooth response with a higher degree of safety.*

predictability

Expect PBI readings to be in the range of 6-10 mcg. %. Count on these readings and on other parameters to be predictable in relation to the dosage you prescribe. Levothyroxine has a high binding capacity for serum proteins in contrast to other thyroid medicaments which may contain varying amounts of L-triiodothyronine which has a low binding capacity. In patients made euthyroid with SYNTHROID (sodium levothyroxine), it is therefore not unusual to find PBI levels of 8-10 mcg. %.

unexcelled dosage flexibility

Available in six strengths. Tablets are scored and color-coded for dosage convenience. SYNTHROID (sodium levothyroxine) INJECTION is also available.

broad indications

SYNTHROID (sodium levothyroxine) duplicates the biological and metabolic activity of endogenous thyroxine. The tablets are specific replacement therapy in diminished or absent thyroid function resulting in hypothyroidism ranging from the subclinical or borderline type to the myxedematous type. The administration of SYNTHROID (sodium levothyroxine) is therefore indicated in primary, hypopituitary, pediatric, and geriatric hypothyroidism, and for reproductive disorders such as infertility, menstrual disturbances and habitual abortion associated with hypothyroidism.

Because SYNTHROID (sodium levothyroxine) is effective in the treatment of hypothyroidism of any degree of severity, it is especially useful in subclinical cases exemplified by symptoms such as undue lassitude, skin disturbances and obesity, in the presence of diagnostic test criteria. In your judgment, when a diminished level of thyroid hormone may be implicated, the purity, stability, and predictability of SYNTHROID (sodium levothyroxine) are particularly important to confirm your diagnosis because they eliminate the variability in response due to product deficiency often encountered with desiccated thyroid.

Precautions: As with other thyroid preparations, an overdose may cause diarrhea or cramps, nervousness, tremors, tachycardia, vomiting and continued weight loss. Medication, in such cases, should be stopped for 2-6 days, then resumed at a lower dose level. In patients with diabetes mellitus, careful observations should be made for changes in parameters that are used to guide antidiabetic therapy. **Contraindications:** Thyrotoxicosis, acute myocardial infarction. **Administration and Dosage:** Administer tablets as a single daily dose, preferably after breakfast. Injection may be administered intravenously in solutions containing 100 mcg. per ml. **Supplied:** Tablets: 0.025 mg., 0.05 mg., 0.1 mg., 0.15 mg., 0.2 mg., 0.3 mg., scored and color-coded, in bottles of 100 and 500. Injection: 500 mcg., lyophilized, in 10 ml. single dose vial, with 5 ml. vial of diluent.

EASY TO PRESCRIBE—EASY TO USE

0.1 mg. SYNTHROID (sodium levothyroxine)
APPROXIMATELY EQUIVALENT TO 1 gr. THYROID U.S.P.

Synthroid®

sodium levothyroxine, FLINT

FLINT LABORATORIES
Morton Grove, Illinois

against the usual gram-negative urinary pathogens

Why use five...where **one** will do?

In a recent 217-patient hospital study,[1] urinary tract infections were treated with a variety of widely prescribed antimicrobial agents including: a sulfonamide (40 patients), chloramphenicol (20 patients), nitrofurantoin (33 patients), nalidixic acid (30 patients), tetracycline (27 patients), colistimethate sodium (22 patients)... and 2 combinations of 5 agents each (45 patients). The 2 combinations were selected to afford maximal theoretical antibacterial coverage against the usual urinary pathogens. They were (1) tetracycline, chloramphenicol, nitrofurantoin, ristocetin and polymyxin B; and (2) tetracycline, chloramphenicol, erythromycin, nitrofurantoin and colistimethate sodium.

This clinical study shows that the two combinations of antibiotics were not superior to some of their single components. The authors point out that antibiotic antagonism often negates theoretical advantages of multiple therapy. Coly-Mycin Injectable (colistimethate sodium) was one of the single components that was shown to be equal to the combinations and eradicated bacteriuria in two-thirds of the patients.

Theoretical choice of multiple antibacterial therapy has been shown to be no more effective than one well-chosen agent which also offers least patient exposure to possible side reactions, toxicities, allergic manifestations and higher drug costs.

1. McCabe, W. R., and Jackson, G. G.: New England J. Med. *272*:1037, 1965.

in gram-negative urinary tract infections often the single well-chosen agent

COLY-MYCIN
INJECTABLE

Coly▲Mycin® Injectable
(colistimethate sodium)

Indications: Especially indicated for the treatment of severe acute and resistant chronic urinary tract infections due to sensitive strains of gram-negative organisms. Also indicated in respiratory tract, surgical, wound and burn infections and in septicemia due to sensitive organisms. Particularly indicated when any of these infections are caused by sensitive strains of *Pseudomonas aeruginosa*.

Adverse Reactions: Occasional reactions such as circumoral paresthesias, tingling of the extremities, pruritus, vertigo or dizziness may occur. Reduction of dosage may alleviate symptoms. Therapy need not be discontinued, but such patients should be observed with extra care.

Warning: Patients should be cautioned not to drive vehicles or use hazardous machinery while on therapy.

Precautions: In cases of impaired or suspected renal impairment, use with greater caution and reduce dosage in proportion to extent of impairment. Transient elevations of BUN have been reported. As a routine precaution, appropriate blood studies should, therefore, be made during prolonged therapy.

As with all polypeptides, the possibility of muscular weakness, including apnea, due to inadvertent overdosage or normal dosage in the presence of impaired renal function, should not be overlooked. In cases of apnea, medication should be promptly discontinued and assisted respiration given until serum levels fall and normal breathing is restored.

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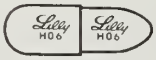	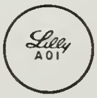	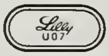	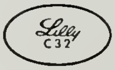	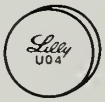

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Echoencephalography: An Evaluation Based on Its Use in 300 Individuals

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THE SEARCH for methods applicable to the localization of intracranial lesions has resulted in the development of a practical apparatus for the identification of midline structures and, therefore, of the displacement of such structures by space-occupying masses.[1–6] The procedure, echoencephalography, is simple to perform and without discomfort to the patient. Since favorable clinical reports[7, 8] have appeared we have attempted to evaluate the limitations within which the results of echoencephalography may be accurately interpreted.

Actually, the apparatus used is, with minor modifications, that applied in the detection of flaws in metal castings. The physical principles of operation depend on the observation that high-frequency, inaudible sound waves will be reflected at varying velocities at the interface of tissues having different acoustic impedance. Part of the sound is absorbed and part is reflected in the form of an echo. If sound strikes a tissue interface at 90° it will be reflected back to its origin. The returning echo may be converted to electrical energy and, in turn, can be displayed on an oscilloscope. In practice, a Polaroid® photograph of the oscilloscope screen provides a permanent record.

The present report concerns our experience with a large number of patients suspected of having an intracranial lesion and presents our views as to the usefulness of echoencephalography.

Materials and Methods

The patient population represents 295 individuals admitted for neurological diagnosis at the George Washington University Hospital and the District of Columbia General Hospital, as well as 5 staff members of these institutions acting as normal volunteers. Except for the latter group, each patient underwent diagnostic study regardless of the results of echoencephalography. The extent of such investigation is reflected in the number of major neurodiagnostic procedures which were performed on the 295 patients: 195 cerebral angiograms, 35 pneumoencephalograms, 20 ventriculograms, and 52 radioactive brain scans.

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Ultrasonic equipment* designed for echoencephalography included use of the Ekoline-20 (Smith, Kline Instrument Company) and the Siemens Echo-encephalograph (Siemens Medical of America, Inc.). A glycerol-water mixture or a water-based gel was used for contact between the transducer and skin. A 1 or 2 mc. per second pulse was applied on the patient's temple directly above the ear with readings obtained at the same point on the opposite side. As experience with the method developed it became expedient on several occasions to obtain paired readings at points anterior and posterior to the usual site. A normal encephalogram is presented in figure 1 and should be compared with the abnormal findings in figures 2 and 3. Although all deviations of the echo from the midline were noted, a 4 mm. deviation was taken as an abnormal value for purposes of this report.

Results

Findings on echoencephalography are presented in 5 categories which indicate the presenting clinical diagnosis (table 1). Particular attention is directed to those instances in which a lesion was not recognized by this technique (table 2).

TABLE 1: Results of Echoencephalography

Group	No. Patients	True		False	
		Normal	Abnormal	Normal	Abnormal
Brain tumor suspects	104	59	34	10	1
Cerebrovascular	84	72	9	3	0
Severe head injury	76	47	20	9	0
Convulsive disorder	25	24	1	0	0
Miscellaneous:					
Normal individuals	5	5	0	0	0
Arteriovenous malformation	2	2	0	0	0
Brain abscess	2	0	0	2	0
Multiple sclerosis	2	2	0	0	0

TABLE 2: Analysis of Falsely Normal Findings

Observation	Tumor	Cerebrovascular	Trauma	Convulsions	Misc.
Shift of 3 mm.	6	1	3	0	0
Bilateral lesion	2	0	1	0	0
Far anterior location	(2)*	0	0	0	0
Normal pneumoencephalogram or angiogram	(2)*	2	2	0	2
No explanation	2	0	3	0	0
Total	10	3	9	0	2

* These observations are also listed as "shift of 3 mm."

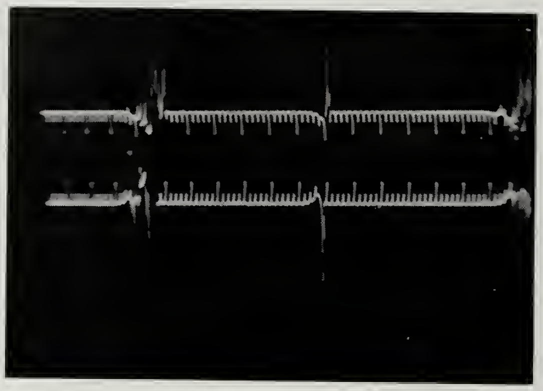

FIG. 1. Normal echoencephalogram. The upper tracing is, by convention, a scan from right to left and the lower tracing from left to right. The outer deflections are due to bone and are often observed as distinct separable peaks due to the inner and outer tables of the skull. The midline echo is represented by the central deflection which is equidistant in each tracing from the outer boundaries.

Brain tumor suspects. Of the 104 patients admitted with the tentative diagnosis of brain tumor 44 actually harbored such a lesion and, of these, 34 were noted to have a displaced midline on echoencephalography. One patient, displaying a shift of midline structures, was found to be free of an expanding intracranial lesion after study by cerebral angiography and pneumoencephalography, the only erroneous positive result in the entire series of 300 individuals. The explanation for the false positive is unknown and the patient remains in good health 2 years after these procedures.

Analysis of the 10 false negative results is instructive. Since a shift of 4 mm. or greater is defined as a significant departure from normal, the echoencephalogram of 6 patients, each of whom displayed a shift of 3 mm., was interpreted as "normal" although, in fact, a brain tumor was present in each instance; a meningioma and a glioblastoma were present so far anteriorly that their effect on spatial relations was minimal in the area at which testing was performed. Another source of inaccuracy in diagnosis was noted in 2 patients with bilateral metastasis to the brain yielding normal records; i.e., the effect of opposing pressures served to cancel any displacement. Two additional patients, 1 with a meningioma of the falx and the other in the olfactory groove, displayed no shift on encephalography and, indeed, none was apparent on pneumoencephalography. Finally, no explanation was found for 2 patients with a cerebral tumor but without a shift on testing. The following are illustrative cases.

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* It is with pleasure that we acknowledge the loan of the instruments for extended periods by both manufacturers.

Case 1. A 44-year-old male alcoholic was transferred from a psychiatric to a medical service with the diagnosis of delirium tremens. A few days after undergoing treatment he was found to be stuporous and hemiparetic on the right side but free of papilledema. An echoencephalogram taken at the bedside revealed a shift of 13 mm. to the right (figure 2). Subsequent angiography was interpreted as being within normal limits. On ventriculography with air and Pantopaque® a tumor was located in the left thalamic area and moderate hydrocephalus was observed. Subsequently the diagnosis was established as that of a glioblastoma resulting in a shift of the third ventricle.

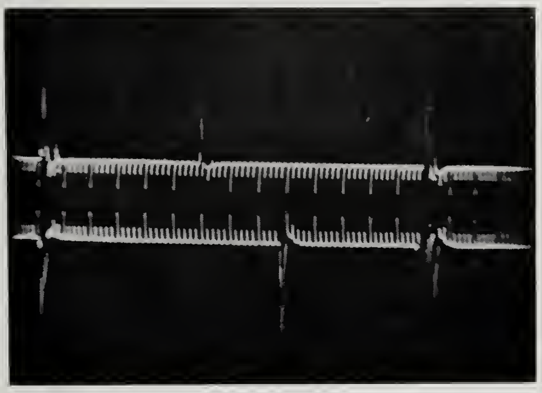

FIG. 2. Glioblastoma in the left thalamic area (case 1) resulting in a 13 mm. shift to the right. Note that the distance from the right outer boundary to the midline echo is the same on both tracings.

Case 2. A 23-year-old Peace Corps member, stationed in South America, was suspected of being the victim of poisoning after the sudden onset of high temperature, headache, drowsiness and diplopia. After transfer to this country he was admitted with the diagnosis of encephalitis. An echoencephalogram (figure 3) revealed evidence for hydrocephalus which was confirmed by ventriculography. The lesion was established as a pontine glioma.

Cerebrovascular group. Of the 84 patients studied, 12 had expanding intracranial lesions of which 9 were located by this method. Of the 3 which were falsely negative, 1 patient with an intracerebral hematoma showed a displacement of 3 mm. Each of the other 2 patients with negative findings had an intracerebral hematoma which was diagnosed on lateral projection of cerebral angiograms; in each case the anterior cerebral arteries, i.e., the arteries in the midline, were not displaced.

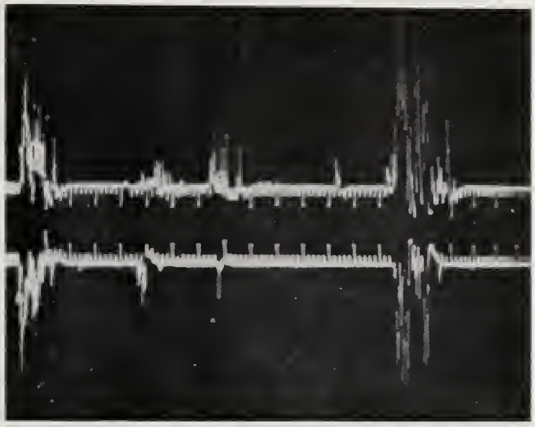

FIG. 3. Pontine glioma (case 2). In this echoencephalogram, particularly in the upper tracing, the walls of a lateral ventricle are shown and were interpreted as consistent with hydrocephalus.

Case 3. A known hypertensive man was admitted in stuporous condition after a grand mal convulsion. Positive findings included right facial nerve weakness, right arm weakness, and sanguineous cerebrospinal fluid under normal pressure. An angiogram was interpreted as being within normal limits. Since the patient's condition improved slightly he was followed conservatively. On the third day after admission he suddenly became more obtunded. An echoencephalogram showed a 7 mm. shift to the right. Without additional neurodiagnostic tests the patient underwent surgery, resulting in the evacuation of a large hematoma from the left temporal lobe.

Serious head injury. In this group are noted the 73 patients subjected to cranial trauma in whom suspicion of intracranial hemorrhage was aroused. Of the 29 patients who actually had an intracranial lesion 20 were located by echoencephalography. The 9 patients with falsely normal recordings included 3 with a 3 mm. shift from the midline, 1 with a bilateral subdural hematoma, and 2 with temporal lobe hematomas which, on angiography, disclosed normal placement of the anterior cerebral arteries. No explanation is available for 3 other patients with subdural hematoma who showed no shift of midline structures by this method.

Case 4. A 29-year-old man was hospitalized following a head injury with resultant drowsiness, right facial nerve weakness, and slight hemiparesis on the right side. Skull X-ray films disclosed a linear fracture in the occipital-parietal area. Bilateral angiograms were obtained because of the suspicion of intracranial hemorrhage but were interpreted as negative. Although his condition improved for the first 5 days after admission, examination on the morning of the sixth day revealed a somnolent man with early papilledema. On echoencephalography a 5 mm. shift from right to left was observed. The patient underwent surgery without further neurodiagnostic studies and 60 ml. of an epidural hematoma was removed from the area directly under the fracture site.

Convulsive disorder. Patients with known epilepsy of many years' standing were originally considered as representing a control group. It was therefore significant that one individual with a 10-year history of convulsions was found to have a shifted pattern on echoencephalography. This finding led directly to other diagnostic studies which disclosed a frontal oligodendroglioma. There were no known false negative studies in this group.

Miscellaneous. Included here are 5 staff members of the department who are presumed to be normal, 2 patients with multiple sclerosis, 2 with arteriovenous malformations, and 2 with brain abscesses. Of these, only the patients with a brain abscess could be expected to be localized by this method; both echoencephalograms and angiograms were normal for both patients, and the abscess was located by ventriculography and radioactive brain-scanning, respectively.

Discussion

It is evident that echoencephalography with the single point or "A-scan" technique employed here is limited to the diagnosis of abnormalities disturbing the normally midline structures and possibly those in which the ventricular system is dilated. The interfaces of such structures appear to reflect ultrasound waves to an extent sufficient to allow recording, although the specific structures actually involved are not always definable. Current evidence favors the walls of the third ventricle[3, 9] or the falx[2, 10] as responsible for midline echoes, but the pineal gland[11] as the source is not ruled out.

Practically, the ability to detect shifts from the midline appears to be a useful if not infallible tool in the neurosurgeon's armamentarium. Of the 88 patients with intracranial masses, 73 per cent were located by electroencephalography, and 92 per cent of all individuals examined were correctly identified; the term, correctly, is taken to imply confirmation on clinical grounds or by use of the usual neurodiagnostic methods. Only 1 false positive was obtained in this series.

Equally pertinent is an examination of those instances in which echoencephalography was falsely normal (table 2). Clearly, revision of the criteria for abnormal recordings is necessary since 45 per cent of the false normals represent tracings involving a shift of 3 mm. It will be noted that the recording scale is subdivided into units of 2 mm., thereby allowing for error in this small range. Therefore, we now use the term "borderline abnormal" for those records displaying a greater than 2 mm. but less than 4 mm. shift from the midline, thereby indicating to the attending physician the need for consideration of further diagnostic procedures.

Many of the falsely negative results were due simply to the very small shift which was actually present. This is borne out by the finding that in 8 such patients either the anterior cerebral arteries were in the midline or the ventricular system as visualized by pneumoencephalography was symmetrical about the midline. Similarly, in 3 patients with bilateral lesions the forces expected to shift midline structures were obviously cancelled by masses on the opposing side.

Although its limitations are apparent, the virtues of echoencephalography are equally obvious. The method is safe and simple, requiring no anesthesia or other compromising stress, and has disclosed intracranial masses not recognized by either angiography or pneumoencephalography. The requirement of only a few minutes to perform the test allows the practical screening of large populations, e.g., that of psychiatric hospitals, and for periodic reëxamination of patients suspected of developing hematomas. Originally conceived as an investigative problem, echoencephalography has proved to be sufficiently successful to allow its use as one of the elements of routine diagnostic study for space-occupying intracranial lesions.

Summary

The technique of echoencephalography as applied to neurodiagnosis depends upon visualization of displaced midline structures and is sufficiently simple, safe and free of stress to the patient to allow its use in the routine diagnostic study of patients with expanding intracranial lesions. In a series of 300 individuals it proved to be 92 per cent accurate; 27 per cent of the records

(*Continued on page 663*)

Evaluation of a Thyroid Analogue in the Therapy of Hypercholesterolemia*

LESLIE ROSE, M.D.†, HAROLD H. ORVIS, M.D.‡, AND NORMAN C. KRAMER, M.D.§

There is substantial clinical interest in the potential usefulness of thyromimetic compounds for therapy of hypercholesterolemia and coronary artery disease. In particular, the dextrorotatory isomer of thyroxine and its analogs have been investigated because of the belief that an adequate and useful separation of their calorigenic and hypocholesterolemic effects may be achieved.[1] However, our first experience with this approach was unsatisfactory in that a majority of angina patients receiving d-triiodothyronine (in a double-blind study) manifested increased symptoms and evidence of hypermetabolism.[2] We, therefore, sought a drug with a relatively greater hypocholesterolemic action for further therapeutic evaluation.

Animal studies with the diethylaminoethanol ester of 3,5,3′ d-triiodothyroacetic acid (herein referred to as d-triac) have shown this compound to have equal or greater hypocholesterolemic effect than that of d- or l-triiodothyronine.[3] On the basis of these data the ratio of minimum effective dose for cholesterol-lowering effect to minimum effective dose for increasing total body oxygen consumption for d-triac is greater than that for l-triiodothyronine by a factor of 10 and greater than that for d-triiodothyronine by a factor of 5. In order to further evaluate d-triac as a potential therapeutic agent for hypocholesterolemia we administered this substance in graded doses to patients without known heart disease. This report summarizes clinical and laboratory observations on 9 subjects treated for 16 weeks.

Method

The subject for this study included 8 patients with known hypercholesterolemia and 1 normal control. None had signs or symptoms of heart disease and each subject was euthyroid as determined by the protein-bound iodine and radioactive iodine uptake tests. Their age range was 33 to 58 years.

After an appropriate control period the subjects were started on 0.1 mg. of d-triac daily. This dose was increased after 2 weeks to 0.5 mg. daily and thereafter by 0.5 mg. every 2 weeks until a maximum dosage of 4.0 mg. daily was achieved or until side-effects prevented further increase.

The subjects were seen biweekly before breakfast for blood sampling and determination of basal metabolism, weight, resting pulse rate, and blood pressure. The basal metabolism was obtained in duplicate with the McKesson Metabolator. Blood lipid determinations included the serum total cholesterol[4] and triglyceride.[5] Three control observations were obtained before initiating therapy. Serum protein-bound iodine determinations, performed by Bio-Science Laboratories‖, and the radioactive iodine uptake test, performed by our clinical laboratory, were obtained before and at the termination of the therapeutic trial.

Results

Two patients were unable to follow the complete regimen. The first, a 37-year-old woman with pretreatment serum cholesterols above 400 mg. per 100 ml., sustained an acute psychotic reaction at a dose of 1.5 mg. of d-triac daily. This episode, preceded by insomnia, headache and anxiety, subsided during 3 weeks of supportive inpatient care. The second, a 47-year-old woman with pretreatment serum cholesterols above 330 mg. per 100 ml., was unable to tolerate a dose higher than 1.2 mg. daily because of excessive nervousness. Sev-

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* Smith Kline & French Laboratories, Philadelphia, Pa., supported this study with a grant-in-aid and supplied the investigational drug.

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eral attempts to raise the dosage to 1.5 mg. daily were unsuccessful. Neither patient exhibited appreciable changes in the serum lipids at these relatively low doses.

Seven subjects completed the therapeutic trial. The blood pressure, pulse rate, and basal metabolism remained relatively constant in each individual. As indicated in table 1, the protein-bound iodine did not change greatly during therapy, whereas a depression in the radioactive iodine uptake averaging −16.7 per cent occurred. More impressive clinically was a loss of weight, occurring in 5 subjects, which averaged 3.8 pounds for the group. A high correlation (r = −.94) was obtained between weight and dose of d-triac. Subjectively 4 out of the 7 subjects experienced increased energy and nervousness.

TABLE 1. Average Results of Therapy in Seven Patients Completing Therapeutic Trial

	Average Pretreatment Value	Average Net Change
Radioactive iodine uptake	24%	−16.7 (range −28 to +9)
Protein-bound iodine	5.1 μg. %	−0.5 (range −1.4 to +1.6)
Weight	172.4 lbs.	−3.8 (range −11 to +3)
Serum cholesterol	280 mg. %	−32.8 (range −146 to +17)
Serum triglyceride	159 mg. %	−34.1 (range −118 to +4)

TABLE 2. Serum Cholesterol and Triglyceride Values from Seven Subjects during Therapy with Thyroid Analogue

Patient	Age/Sex	Control		1.0 mg.		2.0 mg.		3.0 mg.		4.0 mg.	
		Chol.*	Trigly.*	Chol.	Trigly.	Chol.	Trigly.	Chol.	Trigly.	Chol.	Trigly.
1	33/M	280	111	242	91	262	79	254	83	207	87
2	38/M	227	100	280	104	260	101	242	86	210	87
3	53/M	147	132	134	80	170	119	145	78	147	136
4	35/M	288	228	279	149	288	180	282	204	302	188
5	39/M	329	110	295	108	278	93	305	116	304	108
6	58/F	424	109	376	93	301	55	266	61	278	63
7	46/M	268	324	254	301	302	383	266	350	285	206
Average		280	159	266	132	266	144	251	140	248	125

* Average of 3 determinations.

The overall reduction in serum cholesterol was 32 mg. per 100 ml. or approximately 11 per cent of the mean control value, and the overall reduction in serum triglyceride was 34 mg. per 100 ml., or approximately 21 per cent of the mean control value (table 1). There was, however, a relatively low correlation between serum cholesterol (r = −.56) or triglyceride (r = −.40) and dose of d-triac. Detailed serum cholesterol and triglyceride results from the 7 subjects for even mg. doses of d-triac are given in table 2.

Discussion

In experimental studies rabbits fed a diet rich in cholesterol easily developed atheromata; however, rats fed a similar diet did not show the same vessel-wall changes. Katz and Stamler[6] have shown that thyroid hormones are capable of preventing or lessening the atherosclerosis in cholesterol-fed rabbits. This is in conflict with the work of Fisher,[7] who in comparing euthyroid rabbits made hyperthyroid with sodium d-thyroxine and fed the same diet, found more severe atherosclerosis in the hyperthyroid rabbits.

Bernick et al[8] studied the pathology of the thyroid gland in rats and rabbits fed a diet rich in cholesterol. They found a hyperplastic thyroid in the rat, whereas the rabbit thyroid was hypoplastic.

Further elucidation of the role of the thyroid in cholesterol metabolism was contributed to by Duncan et al.[9] They fed euthyroid rats a diet high in cholesterol and found an increase in the mean total body cholesterol concentration. The greatest part of the cholesterol increase was located in the liver. Then they fed hyperthyroid rats the same diet high in cholesterol and found a reduced total body cholesterol which was due mainly to a decreased concentration in the liver. Thyroidectomy caused accumulation of cholesterol in the liver in rats fed the rich cholesterol diet.

The relationship of l-thyroxine and d-thyroxine to hepatic metabolism of cholesterol was studied in the thyroidectomized chick by Lepp et al.[10] They found that the thyroid hormones studied stimulated the hepatic synthesis and release of cholesterol. From the experimental design of their study, they were unable to notice any differences in action of the 2 hormones other than dose required.

The effect of a diet high in unsaturated fats on the plasma cholesterol was studied in hyperthyroid, euthyroid, and hypothyroid rats.[11] It was found that the plasma cholesterol level was lowered by a diet high in unsaturated fats regardless of the difference in levels of thyroid activity. This suggests a different action of dietary fat and thyroid activity in regulating plasma cholesterol.

Experience in experimental animals with thyroid hormones has led investigators to employ a variety of thyromimetic compounds in man in an attempt to achieve an enhanced hypocholesterolemic effect as opposed to the calorigenic effect. Love[12] studied the action of tetraiodothyroformic acid in 29 patients and reported a substantial hypocholesterolemic effect in 69 per cent. Only 27 per cent of the patients exhibited side-effects, and none of these was attributed to increased body metabolism. Corday and associates[13] studied the same compound in 26 coronary patients. Good results were obtained in 16 of 20 patients who were hypothyroid but in only 2 of the 6 euthyroid patients was the blood cholesterol lowered. Good results were also reported by Rabinowitz et al[14] who studied the effects of orally administered dextrothyroxine in hypercholesterolemic euthyroid males. They thought that they were able to separate the cholesterolpenic action of the thyroid hormone from the calorigenic symptoms.

Russek[15] administered d-thyroxine and d-triiodothyronine to a group of patients with clinical coronary artery heart disease. His experience with the former drug was favorable if the dosage was carefully adjusted. With the latter drug he found hypermetabolism in a high percentage of the patients studied. In our clinic several patients had severe cardiovascular reactions during treatment with d-triiodothyronine and its use was abandoned.[2] D-thyroxine was investigated in patients with coronary heart disease by Oliver and Boyd[16] who treated 38 males with electrocardiographic evidence of myocardial infarction or ischemia. It was concluded that a dosage could not be determined which would be certain to lower cholesterol and not provoke angina. This conclusion is similar to that of Jones and Cohen[17] who noted that, although a marked hypocholesterolemic effect might result, therapy with d-thyroxine elevated the basal metabolism, increased the frequency of angina, and aggravated congestive heart failure. These authors indicated that this medication should be reserved for patients free of cardiac symptoms.

In the present study there was noted some decrease in both the serum cholesterol and triglyceride during therapy. This was more prominent in the latter, and it is of interest that changes in these lipid fractions did not necessarily occur together in any given patient. The decline in serum lipids was accompanied by weight loss and symptoms typically produced by thyromimetic compounds. This was not reflected in the basal metabolism, resting blood pressure, or pulse, suggesting that these measurements are not sufficiently sensitive in euthyroid subjects to be of value in guiding therapy.

From this study we must conclude that a separation of the hypocholesterolemic and calorigenic effects was not clearly achieved for the compound employed. Our studies with d-triiodothyronine and d-triac and the experience of other investigators make us doubt that the hypocholesterolemic and calorigenic effects of thyromimetic compounds can be sufficiently and predictably separated to be of general clinical usefulness.

Summary

A dextrothyroid analogue was administered in graded dosages to 9 subjects to evaluate its depressant effect on serum lipids. Calorigenic effects accompanied the modest drop in serum cholesterol and triglyceride that resulted. Therefore, it is concluded that this analogue is unsatisfactory for general use in therapy of hypercholesterolemia.

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Lung Function Tests, Dyspnea, and Work Status*

HAROLD M. SILVER, M.D.†

THE EVALUATION of pulmonary function and its relationship to ability to work are problems which frequently confront the physician when his pulmonary patients ask him to fill out applications for disability benefits or to advise them about continuing their work. This report is a study of the relationship between the subjective complaint—shortness of breath—and the objective findings on pulmonary function tests and their relation to actual work status.

I previously reported on the lung-function test findings and their relationship to the degree of shortness of breath in 100 disability applicants with chronic obstructive lung disease.[1] Those subjects had already made the decision that they were disabled and had made application for Social Security benefits. For comparison I have examined 100 consecutive private patients with obstructive lung disease. In this way a broad physiological, social and vocational matrix was developed, and it is presented to help the physician understand the implications of disability so that he might assist his patients to avoid unnecessary termination of gainful activity.

Methods

All subjects were examined by means of history, physical examination, chest X-ray films, gross spirometry before and after bronchodilators, and electrocardiogram when indicated. Only those with obstructive lung disease who were free of substantial heart disease or restrictive lung disease were included. Spirometry was performed, measuring vital capacity (VC), 1-second timed vital capacity (FEV_1), expressed as per cent of total, 3-second timed vital capacity (FEV_3), similarly expressed, and maximum voluntary ventilation (MVV). Conventional prediction formulae were employed.[2, 3]

The patients were placed in categories based upon the amount of stair-climbing at an "ordinary pace" which they stated they could tolerate. Group 1 consisted of those who could climb 2 or more flights of steps. Group 2 consisted of those who could climb 1 flight of steps before dyspnea supervened. Group 3 consisted of those who could climb less than 1 flight of steps, i.e., ½ flight of steps, before dyspnea supervened. Group 4 consisted of those who could not climb any steps before experiencing dyspnea. The difference between means was assessed by "t" test, using the 5 per cent level of confidence as significant.

Results

Distribution of symptoms. Forty-two per cent of the private patients stated they could walk 2 flights or more before they experienced severe dyspnea and were therefore in Group 1 (table 1). This is in contrast with the disability applicants, of whom only 4 were in Group 1. The remaining private patients were distributed so that there were fewer in the more impaired groups. Thus, the stated degree of dyspnea was less for the complete

TABLE 1: Characteristics of Patients and Applicants

Group	Number		Sex (Male/Female)		Age		Employment Status (Not Employed)	
	Applicants	Patients	Applicants	Patients	Applicants	Patients	Applicants	Patients
1	4	42	4/0	27/15	57.3	50.5	4	2
2	40	34	37/3	20/14	57.0	57.3	40	8
3	50	19	44/6	10/9	56.8	56.2	50	2
4	6	5	6/0	4/1	59.5	62.4	6	4
Total or avg.	100	100	91/9	61/39	57.0	54.5	100	16

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series of private patients than for the applicant series.

Sex. Sixty-one per cent of the private patients were males in comparison with 91 per cent of the applicants (table 1). Of the 39 female patients, 13 were housewives, which indicates that the excess of females in this group is not solely the result of the presence of housewives, an occupation not covered by Social Security.

TABLE 2: Spirographic Data

Applicants versus Patients

Group	VC, Per cent of Predicted		FEV$_{1.0}$ Per cent of VC		FEV$_{3.0}$ Per cent of VC		MVV, Per cent of Predicted	
	Applicants Mean ± SE	Patients Mean ± SE	Applicants Mean ± SE	Patients Mean ± SE	Applicants Mean ± SE	Patients Mean ± SE	Applicants Mean ± SE	Patients Mean ± SE
1	97.6 ± 3.8	93.2 ± 4.0	53.2 ± 7.4	55.1 ± 2.2	84.3 ± 1.7	80.5 ± 2.1	71.5 ± 9.5	62.2 ± 3.6
2	78.6 ± 3.1	81.6 ± 3.5	47.9 ± 1.6	46.2 ± 2.3	77.2 ± 1.5	72.9 ± 2.1	46.6 ± 3.3	46.6 ± 2.8
3	66.6 ± 2.7	71.2 ± 3.5	43.7 ± 1.5	42.7 ± 3.8	72.2 ± 1.8	71.2 ± 3.4	35.1 ± 1.9	36.2 ± 2.6
4	64.8 ± 5.0	54.4 ± 7.9	38.1 ± 3.6	33.0 ± 1.4	68.2 ± 3.7	60.9 ± 2.5	26.5 ± 2.7	23.8 ± 3.8
Total*....	72.6 ± 1.9	83.1 ± 2.4	45.4 ± 1.1	48.6 ± 1.5	74.5 ± 1.1	75.1 ± 1.4	40.6 ± 1.9	50.0 ± 2.2

* (N = 100)

Age. The mean age of patients in Group 1 was slightly lower than applicants in this group, but the ages were remarkably similar in the remaining 3 groups (table 1).

TABLE 3: Spirographic Data

Applicants and Patients Combined

Group	No. Subjects	VC Per cent of Predicted ± S.D.	FEV$_1$ Per cent ± S.D.	FEV$_3$ Per cent ± S.D.	MVV, Per cent of Predicted ± S.D.
1	46	93.6 ± 25.0	54.9 ± 14.1	80.8 ± 12.8	62.9 ± 23.2
2	74	80.0 ± 20.0	47.1 ± 11.7	75.2 ± 11.0	46.6 ± 19.0
3	69	67.7 ± 18.0	43.5 ± 12.6	71.9 ± 12.9	35.4 ± 12.7
4	11	60.0 ± 15.2	35.8 ± 7.0	64.9 ± 8.2	25.2 ± 7.3

Occupation. The private patients included 32 executives or professionals, 40 white-collar workers, 13 housewives, and 15 laborers, of whom only 2 were unskilled. This contrasts with the disability applicant group, which consisted of 76 laborers, half of whom were unskilled, 23 white-collar workers, and 1 professional.

Employment. Sixteen of the 100 patients were not actively engaged in their usual employment (table 1). MVV for these 16 patients was 32.6 per cent. Nine of these were 65 years of age or older and their retirement was obligatory on an age basis. Thus, there were only 7 who were not engaged in their usual occupation solely because of pulmonary disease.

Relation of symptoms to objective findings. The average value of all measured parameters showed a distinct decrease as the stated exercise tolerance decreased (table 2). The trend for decrease in values with increasing dyspnea is statistically significant. In each dyspnea class there was no significant difference between the applicants and patients in any lung function parameter. However, because of the larger number of patients in Group 1, the mean value for VC and MVV of the total patient series was significantly higher than the total applicant series. There was considerable overlap between the individuals in each of the dyspnea groups. Table 3 consists of the total subjects in each dyspnea group, with standard deviation.

Response to aerosol bronchodilators. Spirometry was repeated after the patient had been given isoproterenol aerosol, but occasionally fatigue or excessive cough prevented satisfactory retests. VC increased in 85 per cent of patients and in 77 per cent of disability applicants with satisfactory records. For those who gave satisfactory MVV records, it was increased in 80 per cent of patients, almost identical with the 79 per cent found in disability applicants.

Therapy. Sixteen different forms of therapy are tabulated (table 4). The categories are self-explanatory. Therapy used by the patients prior to initial contact shows several differences from that employed by the applicants. Oral bronchodilators were more frequently used by applicants. Inhalation therapy (modalities 2, 3 and 4) was used to a similar extent by both groups, but the types were not identical. Use of antibiotics was reported more frequently by the patients. The average number of modalities of treatment was 2.0 for the patients as compared with 1.7 for the applicants, a difference which is not statistically significant. Thirty-seven patients and 20 applicants had had no therapy at any time prior to examination.

TABLE 4: Forms of Therapy Employed

Modality	Applicants	Patients
1. Bronchodilators administered orally	52	28
2. Bronchodilators administered by hand nebulizers	35	21
3. Bronchodilators administered by compressed nebulizers	3	17
4. Bronchodilators administered by intermittent positive-pressure breathing	2	7
5. Steroids	12	17
6. Antibiotics	9	35
7. Iodides	13	9
8. Cough syrup	22	27
9. Allergy injections	7	13
10. Bronchodilators administered intramuscularly, subcutaneously, and intravenously	6	6
11. Antihistamines	2	9
12. Oxygen	2	4
13. Breathing exercise	2	1
14. Bronchodilator suppositories	3	4
15. Phlebotomy	2	1
16. Stramonium (asthma cigarettes)	2	2

Discussion

Relationship of lung function tests to stated impairment. Despite the possibility of secondary gain by exaggeration of symptoms in disability applicants there was a remarkable similarity between the lung-function test value and claimed dyspnea in the patients as compared with the applicants. This indicates that when the question of exercise tolerance was carefully worded and not directly related to work applicants gave reliable estimates. It also indicates that when done by a physician with maximum exhortation the disability applicant finally gave as adequate an effort as the private patient, though admittedly more time was required before the record was satisfactory. Two patients failed to give satisfactory MVV after bronchodilators, while 14 applicants failed to do so. Thus, the applicants showed more reluctance to repetition of arduous tasks.

Relation of impairment to disability. When disability is extreme, as in Group 4, in which subjects stated they could not climb any steps and in whom the average MVV was 25 per cent of predicted, all but 1 subject were unable to continue working. Much more interesting, however, is the intermediate zone, represented by Groups 2 and 3, in which 43 of the 53 patients persisted in their usual activity while all of the disability applicants were unable to continue in their usual work. It is in this zone that factors other than objective impairment seem clearly to be related to disability for usual work.

Many previous studies have concentrated on impairment and have tacitly assumed that disability for work was directly related to impairment. For example, Wilson[4] attempted to quantitate pulmonary disability in patients with emphysema. To give a numerical degree of pulmonary disability he devised formulae correlating lung-function test measurements. However, no presentation was made concerning occupation or employment status. Thus, the relationship between the "degree of pulmonary disability" and actual inability to work remains unknown. Similarly, a numerical scale has been proposed by the AMA Committee on Rating of Mental and Physical Impairment, but its "Impairment of Whole Man" table is not validated by either published statistics or experience.[5]

Others have made estimates of the relation of lung function tests to working capacity. Anderson and Schmidt[6] reported that work status was correlated with lung-function tests and suggested that, when the MVV was below 60 per cent of predicted, hard work was no longer possible. Motley[3] regarded an MVV of less than 55 per cent of predicted to indicate severe impairment but did not relate this to work status. Higgins et al[7] stated that it was their clinical impression that those with MVV (indirect) of less than 50 liters per minute are usually definitely crippled by their respiratory insufficiency. Mean values for our patients in Groups 2 and 3 fell below all these estimates but they were able, for the most part, to continue to work. In comparing the work status of patients with that of applicants, biological or treatment differences were evaluated. Since response to bronchodilators was not different, biological variation was not demonstrated by this procedure. Treatment and treatment modalities also did not seem to be sufficiently different to explain the contrast in work status. Therefore, we must inquire as to what factors, other than organic impairment, are involved in producing disability.

Other factors involved in producing disability. The most obvious factor besides physiologic impairment is the energy requirement of work. The physical effort required of laborers is greater, and this may explain why the patients, of whom few are laborers, could continue at their work despite impairment. However, because of the use of labor-saving devices the nominal title of laborer need not indicate high energy requirement.[8]

The second factor which must be considered is motivation. The private patients had jobs which offered more personal satisfaction, higher income, and better social position. These factors tend to make the option of disability far less attractive. Others who have studied the relationship of impairment to work status in pulmonary patients have also found socioeconomic level or motivation to be important determinants.[8, 9]

Medical advice may be an important factor in the patient's "decision to be disabled." The physician's attitude, as well as his counsel, conveys to the patient either hope or pessimism about continued work.

Implications for disability determination. The lung-function tests provide a convenient estimate of physiologic impairment for disability determination. Table 3 is a guide to the relation between dyspnea and ventilatory tests. Approximately two-thirds of the values should be the mean plus or minus 1 S.D. If there is any great discrepancy between the amount of dyspnea claimed and the profile exhibited in table 3 the possibility that all the symptoms are not explained by the ventilatory impairment of obstructive lung disease should be entertained. Other factors such as impaired ventilation perfusion relationships, restrictive lung disease, heart failure, and malingering or denial must then be considered, and further clinical and laboratory investigation may be in order.

The physician is on relatively solid ground when he limits his estimate to impairment. Often, however, a statement as to disability is required and a precise definition as to what constitutes disability is not provided. Definition of disability is usually a legal or administrative usage, and it is probable that lack of precise definition reflects both the difficulty of creating precise scientific definitions as well as a reluctance to lose the flexibility and responsiveness to social climates which ambiguity permits. This ambiguity is apparent in forms which inquire whether the patient is "capable of doing his usual activity" or of "doing any activity." Qualifications such as "without extending himself," "by extending himself moderately," or "by extending himself maximally" might help to give a frame of reference but are not provided. The Social Security Act definition of disability is "inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or has lasted or can be expected to last for a continuous period of not less than 12 months." A booklet explaining the rules indicates that "the reporting physician is not put in the position of having to decide whether or not his patient is disabled," and it is frankly stated that the decision as to disability is administrative.[10] This recognizes the key role of the interpretive element in disability determination.

Social factors may have a pronounced effect, not only in defining but quite possibly in producing disability. These social influences may be paradoxically pluralistic. Attitudes which encourage continued activity emphasize the desirability of personal independence and productivity and are reflected in education, training, comprehensive vocational rehabilitation programs, and in the energetic use of all means to direct persons with vocationally significant impairments into such programs. Rigorous impairment requirements and low disability benefits may tend to encourage continued activity. At the same time, sincerely humanistic attitudes in society, which promote the minimization of financial consequences of disability by high disability benefits, easy impairment requirements, and the full use of information media and social services to initiate and assist in the filing of disability applications may tend to foster disability. This pluralism is probably inherent in our society. The balance implied therein is healthy, but excesses in either direction may be unhealthy.

The physician's role. As physicians, we have the opportunity to be of real value to our patients in maintaining employment and in encouraging rehabilitation. We do this first by being good doctors who make the correct diagnosis and give informed treatment. We should not hesitate to ask for expert help when needed in order to elucidate the diagnosis, quantitate impairment by means of lung function tests, or give the best treatment. We have a need to continue our education and to read recent publications such as "Management of Chronic Obstructive Lung Disease"[11] which was recently provided all of us. It is important to explain the nature of the disease to the patient as well as to his employer at times so that a more encouraging attitude is presented. When we handle the temporary setbacks which may be induced by infection, heart failure, or other reversible situa-

(*Continued on page 702*)

Duration of Allergy to Antituberculous Drugs (PAS, SM and INH) in Tuberculous Patients

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During the past decade on the tuberculosis service of a veterans hospital in West Virginia occasional instances of allergy to the antituberculous drugs, para-aminosalicylic acid (PAS), streptomycin (SM), or isonicotinic acid (INH), were observed. The patients, ill with pulmonary tuberculosis, developed allergic manifestations 1 to 6 weeks after starting for the first time a course of PAS, INH or both. The signs and symptoms included fever, dermatitis, hepatitis with enlargement of the liver and jaundice, generalized lymphadenopathy with enlargement of the spleen, increased cough with pulmonary infiltration, and the presence of atypical leukocytes (Türk cells) in the circulating blood. Three of the patients, studied in detail in 1955, were found to give positive patch tests to the culprit drug.[1] Since then all the tuberculous patients showing generalized signs of drug allergy have been patch-tested. Of these, ⅕, comprising those with severe generalized eruptions, gave positive patch tests.

Since it was not known how long such sensitivity might persist, every patient who had suffered a generalized reaction to one or more of these antituberculous drugs and who had demonstrated positive patch tests to the suspected culprit drug was patch-tested again for drug allergy over a period of 2 to 9½ years. The purpose of this paper is to describe the results of such follow-up studies.

Materials and Methods

Patients. The 14 patients were male veterans between the ages of 24 and 67 admitted to the tuberculosis service for the treatment of pulmonary tuberculosis. In every case the chest X-ray film was typical of infiltration by *Mycobacterium tuberculosis*, and the organism was cultured from the sputum. On admission most of the patients were febrile and appeared generally ill. Within a few days of admission, as soon as the diagnosis appeared certain and the sputum had been sent for animal inoculation and culture, the patients were started on a regimen of at least 2, and often 3, antituberculous drugs, usually PAS and INH, and occasionally streptomycin as well. The doses were the usual ones prescribed: PAS 4 Gm. q.i.d., INH 100 mg. t.i.d. orally, and SM 1 Gm biweekly intramuscularly. None of the patients had received antituberculous therapy previously. None had a family history or past history of significant allergy.

One to 12 weeks (on the average 3.8) after beginning drug therapy the patients developed fever, an eruption which gradually became generalized, jaundice, enlargement of the liver, and occasionally of the spleen. Some patients also developed generalized lymphadenopathy, others an exacerbation of cough. One patient developed acute arthritis of the joints of all extremities. In addition to these typically allergic symptoms, the patients complained of malaise, headache, and intense itch. A few patients were ill to the point of prostration. In these cases the eruption was so extensive that the entire body appeared edematous.

Laboratory. Upon admission a few patients showed a mild anemia, but the hemogram otherwise was normal and no cases of hemolytic anemia were encountered. In general, during the course of the drug reaction the hemoglobin and hematocrit remained unchanged. The white blood cell count was usually increased, varying from 11,000 to 68,000. Eosinophilia usually became evident, varying from 8 to 66 per cent. Abnormal lymphocytes (Türk irritation cells) were regularly present, but L.E. cells were not seen. In 3 cases chest X-ray films revealed an increase in infiltration, spreading somewhat fanlike from the original lesions. These infiltrates disappeared within a few weeks as the drug reaction subsided. In 1 case eosinophilia was demonstrated in the sputum.

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Liver function studies were abnormal in every patient who became jaundiced and/or developed hepatomegaly, the thymol turbidity test reaching a peak of 14, the cephalin flocculation test ++++, transaminase 183 units, bilirubin 4 mg. per cent direct and 7 mg. per cent indirect, and alkaline phosphatase 45 Bodansky units. In every case the eosinophilia and abnormal hepatic function tests returned to normal within 2 to 16 weeks following discontinuance of the drug.

Schedule for testing. The patient was patch-tested with the suspected drug, usually para-aminosalicylic acid, streptomycin, and isoniazid as soon as he was considered to be recovering from his generalized allergic reaction, i.e., when the fever had largely abated and the jaundice and eruption were subsiding. This event occurred usually between the fourth day and the fourth week. Thereafter patch tests were applied after a 2-month interval, then at 6-month intervals insofar as possible. Most of the patients, after they had gone home, returned every 6 months for follow-up chest X-ray films and sputum studies. The patch tests were applied upon readmission so that they could be read 48 hours later at the time of the patient's routine follow-up discharge from the hospital.

Method of patch-testing. A site on the lateral aspect of the patient's arm was cleansed with alcohol and allowed to air-dry. A saturated solution of the suspected drug was made by pulverizing a tablet in the smallest amount of water in which it was soluble. This solution was used to dampen a small square of gauze which was applied to the cleansed area, covered with adhesive tape, and labeled. A similar patch dampened with saline was used as negative control. In addition, another patch moistened with a saturated solution of some other drug (as phenobarbital, insulin, Zephiran®, or Dilantin®) was applied as another control. (Whenever a patient was thought to be allergic to adhesive tape, the patch was secured with Scotch tape or with a bandage.) Whenever a drug was supplied in liquid form, as Nydrazid®, it was dropped on the gauze patch. The tester carefully washed her hands between the application of each test.

Forty-eight hours later the tests were read as follows:

1 plus: induration, redness and swelling in a square area under the gauze patch with normal skin surrounding. No vesicles were present.

2 plus: scattered small vesicles on the indurated area

3 plus: many vesicles, almost contiguous

4 plus: confluence of the many small vesicles into 1 large bleb.

Spread of redness, swelling and induration of the skin beyond the patch was simply described as such or in the table marked as 5 plus.

Duration of follow-up. It was hoped that patients could be patch-tested every 6 months for at least 5 years. However, many patients were lost to the study for a variety of reasons, principally because of acquiring a job in another state. Two patients died during the course of the study. This report deals only with those who could be followed 2 to 9½ years.

Since the history and clinical course of the patients were remarkably similar with only minor variations, it would seem repetitious to describe each individually. A case report typical of the group follows:

R. McC., a 48-year-old accountant, was admitted in June, 1956 because of a chronic cough. Chest X-ray films in 1951, 1952 and 1953 had been negative. In 1954 the chest X-ray film was said to reveal a "scar on the lung," but the patient did not return for further evaluation. In 1956, because of weakness, night sweats, a weight loss of 30 lbs., increasing cough and sputum, the patient returned for X-ray follow-up. He was found to have tuberculosis and was hospitalized on June 27, 1956.

The family history disclosed no evidence of allergy.

The patient had received penicillin, aspirin, and other medication on various occasions in the past without adverse effect.

Physical examination showed a small, thin, tremulous man who appeared chronically ill. He was oriented and coöperative. Dullness was percussed in the right apex posteriorly. Breath sounds and voice sounds were increased and of bronchial quality over both apices where scattered crackling rales were heard. The heart sounds were only slightly decreased in intensity.

The hematocrit was 38 and the white blood cell count on admission 13,500 with 93 per cent polymorphonuclears and 3 per cent lymphocytes. Within a few days the leukocytes had decreased to 8,000. The blood urea nitrogen, total protein, A/G ratio, serum bilirubin, and cephalin flocculation were within the normal range. The thymol turbidity was 2 units and the sputum revealed acid-fast organisms. Urinalysis and serology were negative and remained so throughout the period of hospitalization.

X-ray films of the chest showed irregular patchy clouding in both upper and midlung fields. There was a cavity on the left and honeycombing on the right.

The clinical impression on admission was pulmonary tuberculosis, bilateral, far-advanced and active.

On June 30, 1956 the patient was placed on a regimen of PAS, Gm. 4 t.i.d., INH, 100 mg. t.i.d., and SM, 1 Gm. daily. All went well until July 20, 1956, when he developed chills and a fever of 105° after each injection of SM. Within a few days he developed a generalized dermatitis and jaundice. His liver was palpable. All drugs were discontinued, and the fever subsided within 24 hours. The leukocyte count reached 30,000 with 25 per cent eosinophils. Numerous Türk cells were identified. Liver function studies showed an alkaline phosphatase of 12.5 units, transaminase 43, cephalin flocculation ++++, and bilirubin 3.8 mg.

As soon as the leukocyte count and liver function tests had begun to return to normal the patient was given a therapeutic test of 1 dose each of the following drugs at 3-day intervals:

1. PAS, which caused gastrointestional distress and an eruption within 24 hours,
2. SM, which caused fever and chills within 2 hours, the reaction subsiding within 24 hours, and
3. INH, which was well tolerated.

Thereafter INH, 100 mg. t.i.d., was added to his therapeutic regimen. By mid-August the liver function tests had returned to normal, and pyrazinamide was added as well.

Patch tests with saturated solutions of the drug gave the following results:

PAS	++++ with huge vesicle
SM	++, 3 papules on raised indurated square base
INH	negative.

The positive tests subsided slowly and at the end of 2 weeks were still visible and palpable. At this time it was concluded that PAS had caused the eruption, and SM the fever and chills.

An attempt was made to increase the patient's tolerance to SM. He was given gradually increasing doses (0.05 c.c., 0.1 c.c., 0.15 c.c., etc. to 0.50 c.c.), starting with a dilution of 1:10,000. All went well through the 1:1,000, 1:100, and 1:10 dilutions. Full strength SM was reached in June 1957 without mishap, and on July 2 the patient received 1.0 Gm. intramuscularly. Twelve hours later he developed a plaque-like eruption above the alae of both ilia and a pruritic erythema of the face and neck.

Since the patient seemed to tolerate all but the highest doses of SM, it was decided to give 0.5 Gm. doses every second day. During the first 8 hours after every dose the patient felt anorexic, and 6 to 8 hours after the injection he became dyspneic. The dyspnea lasted 36 hours. Despite reducing the dose to 0.40 Gm. twice weekly the eruption increased, especially on exposed areas, and vesicles developed on the hands. Therefore SM was discontinued, but PZA and INH were continued.

The patient did well during the ensuing 8 months. He gained in weight and strength; his sputum became negative for acid-fast bacilli, and he was discharged in March 1958. All laboratory values had returned to normal, including the bromsulfalein test. He returned once or twice a year for follow-up studies.

Results of testing. As shown in table 1, 14 patients were followed for 2 to 9½ years. All 14 gave positive patch tests to PAS, 3 to SM, and 7 to INH when first studied. Of those allergic to PAS 3 became negative within 2 years and 1 within 3½ years. The other 10 gave positive patch tests when last tested at intervals ranging from 2 to 9½ years after the first test.

Although the test antigens were freshly prepared before the tests were applied, some patients with the passage of time apparently became less sensitive. One patient (no. 3 in table 1) when first tested with PAS diluted 1:500 gave a +++ reaction. Years later this dilution produced a negative test, but full strength PAS produced a 1 plus reaction.

Of the 2 patients allergic to SM by patch test, 1 gave a negative test 8 months later, the second remained positive for at least 2 years.

Of the 7 patients who initially gave positive patch tests to INH 2 became negative within 2 years, and the remainder were positive when last tested 2 to 6 years later.

Another patient (no. 13 in table 1) who developed fever and chills upon ingestion of INH gave a negative patch test initially. When retested 2 years later he had developed a positive test even though INH had been discontinued early in the course of therapy. During this time the reaction to PAS did not change.

Discussion

Adverse reactions to PAS, SM, and INH have been well documented for the better part of 2 decades, and hundreds of references are available.[2–5] In many reports no attempt was made to distinguish between toxic and allergic reactions.

Drug allergy usually can be detected in 1 or 2 ways.[6] The first is by demonstration of antibodies in vivo or in vitro. Examples in vivo are seen in the skin test (puncture,[7] scratch, intracutaneous, or patch[8]), in passive cutaneous anaphylaxis in laboratory animals,[9] and in humans in overdose reactions to administration of antigen.[10] Examples of in vitro tests are precipitation, gel diffusion, hemagglutination, complement-fixation, etc. wherein various physical and chemical effects of antigen-antibody interaction result in visibility.

The second way to detect drug allergy is indirect[6] by demonstration of symptoms that are typical of allergy to any well-studied antigen. Since the symptoms have been produced by antibodies formed to a known antigen it is presumed that the symptoms can be produced by antibodies to a drug antigen. If the resultant symptoms are not life-threatening to the patient the drug can be

TABLE 1. Clinical and Patch Test Data on 14 Patients Allergic to Antituberculous Drugs

Patient	Age	Drug Causing + Patch	Date of Generalized Reaction	Length of Time on Drug before Symptoms (weeks)	Date of First + Patch	Total + Patch Tests	Years Followed	Final Tests	Interval after Which Tests Negative	Clinical State
1. McC	48	PAS ++++ SM 0 INH 0	1956	3	Mar. 57	6	9½	PAS +++ SM 0 INH 0	Remained positive	Well, working, tolerated PZA* and INH
2. Car	52	PAS ++ SM ++ INH ++++	1959	4	Oct. 59	2	3	PAS 0 SM 0 INH 0	PAS 3⅓ years. SM ⅔ yr. INH 2 yrs.	Well, tolerated SM and PAS
3. And	50	PAS 1:500 ++++ SM 0 INH +++	1959	4	Dec. 59	6	5	PAS 1:10 + SM 0 INH ++	Remained positive 5 yrs.	Well, retired, tolerated CS† and viomycin
4. McK	65	PAS ++++ SM 0 INH +++++	1959	5	Sept. 59	5	2	PAS ++ SM 0 INH +++++	Tests remained positive	Died 1962
5. Han	24	PAS 1:100 ++++ SM 0 INH 1:100 ++++	1959	5	Aug. 59	5	6	PAS 1:10 ++ SM 0 INH 1:10 ++	Remained positive but less strongly so	Well, physical work, tolerated SM and PZA
6. Wel	57	PAS ++++ SM 0 INH 0	1958	12	Feb. 61	2	2	PAS ++++ SM 0 INH 0	Remained positive	Moved to Kentucky
7. Mur	29	PAS +++ SM 0 INH 0	1961	3	Mar. 62	3	2	PAS 0 SM 0 INH 0	2 yrs.	Well, sputum negative
8. Mar	67	PAS ++++ SM 0 INH 0	1963	1/7	July 63	2	2	PAS + SM 0 INH 0	Remained positive	Tomato vine contact dermatitis whenever exposed
9. Mil	44	PAS +++ SM 0 INH ++	1964	2	Sept. 64	3	2	PAS 0 SM 0 INH 0	2 yrs.	"Desensitized," tolerated INH, CS and PZA
10. Pay	55	PAS ++ SM 0 INH ++ Dilantin ++	1964	2½	Sept. 64	3	2	PAS ++ SM 0 INH ++	Remained positive	Improved, sputum negative
11. Bla	55	PAS ++ SM 0 INH 0	1963	3½	Oct. 63	3	3	PAS 0 SM 0 INH 0	Decrease in 6 mos., negative 2 yrs.	Working as bartender, tolerated PAS and INH
12. Mal	49	PAS ++ SM +++ INH 0	1964	3	July 63	2	2	PAS ++ SM +++ INH 0	Remained positive	"Desensitized" INH, tolerated PZA and CS
13. Klo	50	PAS ++++ SM 0 INH 0 (fever and chills)	1962	3	Jan. 62	2	2	PAS ++++ SM 0 INH ++	Remained positive	Died October 1964
14. Bo	38	PAS ++ SM 0 INH ++	1963	3	Feb. 63	2	2	PAS ++ SM 0 INH ++	Remained positive	Well, working

* PZA—pyrazinamide † CS—cycloserine

readministered and withdrawn. If symptoms occur only on administration of the drug and subside upon its being withdrawn it is highly likely that the drug (or one of its degradation products) is the cause of the reaction. Readministration does not differentiate between toxic and immunologic symptoms, since the symptoms recur in both cases. However, in allergy the symptoms are reprecipitated usually by a tiny dose (because the antibodies have already been formed), and the symptoms recur at shorter and shorter intervals after each readministration of the antigen (drug).

In this paper both of the above methods of demonstrating drug allergy were used. Antibodies in vivo were demonstrated in every patient by the patch tests. In every case wherein readministration was considered safe the patient promptly redeveloped the original symptoms.

The 14 patients demonstrating positive patch tests to the incriminated drug(s) represent only a small percentage of the total number of hospitalized tuberculous veterans exhibiting some sort of untoward symptom to their antituberculous medicine. Most of these patients were not patch-tested because their symptoms were not typical of allergy. Of those whose symptoms suggested an allergic origin most gave negative patch tests. In general these patients seemed to be less severely ill than those that gave positive patch tests. Of the latter, most, for reasons beyond our control, could not be restudied at regular intervals for a period of years. Hence, the 14 patients are culled from a much larger group and probably represent the severest cases.

The patch test depends upon the presence of cellular antibodies reacting with the antigen, in these cases PAS, SM, or INH in the epidermis. In the patient's allergic reaction the antigen reaches the antibodies via the blood stream since the same symptoms were produced whether the drug was ingested (PAS and INH) or injected (SM), and no cases of contact dermatitis occurred spontaneously in these patients. Upon application of the patch test the antigen is absorbed into the cells of the epidermis, reacting with the already-formed antibodies to the drug.

In occasional cases of drug allergy circulating antibodies have been demonstrated. In the cases reported here circulating antibodies were not demonstrated, although a detailed study of them was not made in every case.

That these delayed allergic reactions were specific is shown by these facts:

1. Normal hospital personnel and patients not receiving the antituberculous drugs gave negative reactions in every case.
2. Tuberculous patients receiving the drugs but suffering no symptoms therefrom gave negative patch tests, even after years of drug therapy.
3. The tests were consistent and could be repeated several times at monthly intervals without demonstrable change in the patient's reaction.
4. Only those patients receiving the drug and having symptoms at the first testing gave positive patch tests.
5. Patients on high doses of prednisone gave diminished tests, but when prednisone was discontinued patch tests became clearly positive. These results are consistent with the effect of steroids (prednisone) on the delayed skin test.
6. Antihistaminics ingested t.i.d. or q.i.d. had no effect on the patch tests. Antihistaminics are known to decrease the immediate type of skin test but do not influence significantly the delayed type of skin test.

The patch test was remarkably constant, the same results being produced in the same patients by different testers at different times, even when the patient had been placed on a different regimen of diet and/or medication.

None of the veterans giving positive patch tests showed signs of drug toxicity. For example, those taking INH showed no signs or symptoms of peripheral neuritis; those on SM did not experience headache or tightness about the mouth.

The differentiation between toxic and allergic reactions to drugs is particularly important in cases of hepatitis, with or without jaundice. Since every patient had normal urinary findings and liver function tests on admission, and since PAS, SM and INH are not unduly toxic to the liver (as, e.g., pyrazinamide), the hepatitis can be attributed to drug allergy.

The fact that these veterans had neither a family nor past history of asthma, hay fever, or urticaria suggests that this type of drug allergy is not influenced by heredity. None of these patients had experienced an untoward reaction to penicillin or aspirin, although each had received both drugs previously on several occasions.

All of the patients denied having previously taken any tuberculous drugs. In 1 case, no. 8 in table 1, this information sounds doubtful, since the patient developed fever and eruptions 24 hours after his first dose of PAS. If his patch test had been negative, one might have supposed that the symptoms were toxic or occurring on some basis other than allergy, but the patch test continued to be positive 2 years later. The explanation may be that the patient had developed antibodies to an antigen (similar to PAS) metabolized from some previously ingested food or drug which cross-reacted with PAS.

The patients who complained of fever, headache, chills and other symptoms but who exhibited no eruption gave, without exception, negative patch tests. Many of the patients, however sick, who developed localized eruptions covering only part of the body gave negative skin tests. It appeared that only those patients with generalized eruptions (±other symptoms) showed positive patch tests. Whether this fact is related to the severity of the symptoms or to the amount of antibody, or to other factors, is not known. SM frequently caused fever, chills, and cyanosis within 12 hours even though the patch test remained negative. The patients suffering with drug fever but without dermatitis never gave a positive patch test.

Infrequently a patient experiences symptoms before antibodies can be demonstrated. Case 13 appears to be such an example. The patient had fever, chills, and a generalized dermatitis when being treated with PAS, SM and INH. As can be seen in table 1, patch tests were positive to PAS but negative to SM and INH. When PAS was discontinued the eruption subsided but chills and fever continued. Upon discontinuance of INH the patient became afebrile. He tolerated SM and other drugs without difficulty. Two years later, while the test to PAS was still positive, the patient was found to have developed antibodies to INH. It is unfortunate that tests could not have been done at regular intervals in the meantime to see when antibodies to INH became demonstrable.

PAS and INH have closely related chemical configurations; both are small molecules with reactive amino groups which may readily act as haptens. Their structure may explain the longer duration of sensitivity that they evoke compared with SM, which has a different chemical configuration and which less frequently causes hypersensitivity of similar pattern and duration. The fact that PAS competes with INH for acetylation[2] accentuates the importance of its metabolism in inducing antigenicity.

One patient (no. 2, table 1), after his skin test to PAS had become negative, was challenged with a test dose of the drug. No symptoms developed. Thereafter he was able to tolerate a prolonged course of PAS without recurrence of allergy. It would be interesting to know if toleration of the drug is usual in patients whose antibodies have subsided. Those patients who retain some degree of sensitivity (a low level of antibodies) may be those who develop an anamnestic reaction when the drug is readministered after an interval. Further studies are necessary to answer this question.

The patch test, then, may be useful in demonstrating some types of hypersensitive reaction to some drugs and helping to determine when the drug may safely be readministered to a patient requiring it but who has been allergic to it.

Since the patch test is easy to perform and its results clear-cut, internists, who encounter drug reactions, might more frequently avail themselves of this test. If a control test of saline is applied the results are easy to read, provided of course that for the patient's safety the eruption is decreasing or has subsided and nontoxic or nonirritative drugs in suitable concentration are used. The exact time necessary for the development of cellular antibodies has not been studied in detail in relation to many drugs.

Summary

Fourteen patients exhibiting severe allergic symptoms to antituberculous drugs (PAS, SM, INH) gave positive patch tests to the drugs—all 14 to PAS, 2 to SM, and 8 to INH.

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When the drug was withdrawn and the patient retested at 6- to 12-month intervals the positive tests persisted in most cases for years.

There was a tendency for positive tests to decrease with time.

PAS produced a high proportion of positive tests persisting for several years. At the end of 2 years only 3 of 14 had become negative. At the end of 5 years 3 still gave positive tests. The longest follow-up was for 9½ years, at which time the test still remained positive.

Of the 2 positive patch tests to SM, 1 had disappeared within the first year, the other remained unabated after 2 years.

Of the 7 patients initially giving positive patch tests to INH, 2 became negative within 2 years, the others remained positive for 2 to 6 years.

Drug allergy to PAS and INH tends to be of long duration. Although the number of cases is not comparable, it would appear that PAS and INH hypersensitivity of the type described tends to last longer than does SM hypersensitivity.

Drug allergy is often difficult to prove. The patch test is useful to diagnose the type of generalized allergic reaction produced by PAS, INH, and occasionally SM when generalized dermatitis is prominent. It is not useful in drug fever alone, or in reactions of lesser severity, or of milder and localized dermatitis.

(Continued on page 668)

Tegretol (Carbamazepine): A New and Effective Medical Treatment of Trigeminal Neuralgia, with a Note Concerning Its Use in the Syndrome of Thalamic Hyperpathia*

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UNTIL VERY RECENTLY the condition known as trigeminal neuralgia or tic douloureux, agonizingly painful in nature and baffling in etiology, has responded in satisfactory fashion only to neurosurgical treatment. Vitamins B_1 and B_{12}, by mouth or injection, have afforded temporary relief for reasons unknown, not as a therapy of real nutritional deficiencies. Inhalations of trichlorethylene and systemic administration of stilbamidine have also been effective on a short-term basis, apparently because these 2 compounds are toxic to the trigeminal nerves or ganglia and produce a transient form of "medical surgery." Pure analgesics of any type can of course suppress appreciation of this form of pain as they do that of any other but usually not to a significant degree. Vasodilating drugs such as Priscoline® or nicotinic acid seem to help a rare patient. The known tendency of tic douloureux to disappear spontaneously for unpredictably varying lengths of time confuses the evaluation of any medical therapy in this strange disease.

Apparently on a purely empiric basis Dilantin® (diphenylhydantoin) was introduced into the medical treatment of trigeminal neuralgia in the 1940's.[1] It has proven to be effective in about 50 per cent of cases, only in high dosage and in the experience of many,[2] myself included, but must often be abandoned because of severe toxicity. A combination of Dilantin with Tolseram® (mephenesin carbamate) may be more effective than the hydantoinate alone, but an additional source of unpleasant side-effects is added. Tolseram itself has been administered as a primary antineuralgic medication, and the results recently reported from its use will be referred to later. The known anticonvulsant properties of Dilantin naturally suggest a central nervous effect of this medication in damping paroxysmal pain, and experimental studies have shown depression of trigeminal reflexes at the level of the brainstem in decerebrate cats.[3]

The success, even if only partial, of one anticonvulsant medication prompted trial of another, Tegretol (carbamazepine). Tegretol is not related to the hydantoins but resembles Tofrānil® (imipramine). Blom[3] on the basis of his own experiments became aware of the similarity of the inhibition of brainstem reflexes by this drug to that exhibited by Dilantin. In 1962 he made the first report of consistent success in the control of trigeminal neuralgia by medical means, by the use of carbamazepine. Since then many investigators in Europe[4-7], Australia,[8] and latterly in the United States of America[9, 10, 11] have reported series of cases of patients treated for tic douloureux with Tegretol, and the degree of success although variable is consistently high. The length of time during which such reported good results have held up indicates that the application of carbamazepine in the treatment of painful tic does indeed represent a "major breakthrough" and not just another coincidental use of medication during periods of spontaneous remission in an unpredictable disease.

Experimental studies of Tegretol in conscious animals indicates that the drug has a certain selectivity on the neurons involved in central transmission of trigeminal pain impulses, resulting in presumed clinical depression of painful circuits at the medullary as well as the thalamic levels.[7]

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* This study was undertaken as part of a research project (N274-11-65) sponsored by Geigy Pharmaceuticals, Yonkers, New York, the manufacturers of Tegretol (carbamazepine, G-32883, 5-carbamyl-5H-dibenz [b, f] azepine hydrochloride) and was directed by Dr. T. P. S. Watts of the Medical Department of Geigy, who kindly supplied the medication used free of charge to patients.

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Drowsiness, dizziness, and unsteadiness of gait are uncommon but frequently reported side-effects of Tegretol administration, are usually transient, not incapacitating, and infinitely preferable to lancinating pain, and almost always disappear with the reduction in level of dosage. Dermatitis occurs rarely.[6] One fatality from aplastic anemia has been reported after Tegretol administration.[12] In general, therefore, the toxicity of carbamazepine, considering the great number of patients who have received it, not only for trigeminal neuralgia but also in the primary treatment of epilepsy over a period of years, is not greater than that of any other anticonvulsant drug and less than the toxicity of many.

Notwithstanding the good reports from abroad, however, the Food and Drug Administration of the United States Government, proceeding in this area as well as in many others with understandable caution, has not extended its complete approval to Tegretol as yet but has permitted its use on a clinical experimental basis. The following report concerns a series of patients treated with Tegretol for trigeminal neuralgia and allied conditions and a small group of sufferers with the "thalamic syndrome" (thalamic hyperpathia of Dejerine-Roussy), the effects upon whom may be of equal interest.

Materials and Methods

Tablets of Tegretol (200 mg. carbamazepine) were administered 2 to 4 times per day after meals to consecutive patients suffering from primary or recurrent trigeminal neuralgia, other varieties of facial pain, and thalamic dysesthesia without selection of patients. Clinical examination, blood counts and tests of liver function constituted control inspection during the time of testing. Many of the patients had been treated by surgery or injection of alcohol into various branches of the trigeminal nerve or the gasserian ganglion.

The medicine was administered directly from my office in order to control the supply and to make sure that the patients were taking the pills in the manner decided upon.

Results of these clinical trials are summarized in table 1.

Results

It will be seen at once that results of the medical therapy of classical trigeminal neuralgia (tic douloureux) in this series of cases were excellent (100 per cent benefit) at a low level of medication and whether patients had received preceding surgical therapy or not. The almost unbelievably rapid effect of 1 or 2 tablets was notable as has been reported by many others.[6] Many patients preferred to use the drug intermittently simply because they found regular dosage not to be necessary. Although the longest follow-up in this series is 7 months, this report is corroborative of previous, longer-term series cited previously. Only 1 patient (case no. 12, C. Z.) was forced to discontinue Tegretol intermittently because of toxicity but reported excellent benefit in terms of relief from pain nonetheless. No patient developed signs of depression of function of the liver or bone marrow.

Percentages of patients with tic douloureux reported to have been relieved of pain completely by the use of Tegretol in other studies reported vary from 68 to 100 per cent after many months to several years of observation under treatment. The majority of successes in published communications are in the 85 to 100 per cent range.[4, 5, 6, 8, 11, 13] This contrasts favorably with another very recent article concerning the response to long-term medical treatment of trigeminal neuralgia with another medication, Tolseram (mephenesin carbamate)—only 60 per cent acceptable benefit without surgery.[14] There would appear to be no difference in toxicity between the 2 drugs.

Attempted treatment with Tegretol of severe postsurgical paresthesias, postherpetic neuralgia of the face, multiple sclerosis with symptomatic trigeminal neuralgia, and atypical facial neuralgia was unsuccessful in this series as it had been reported to be by others.[4, 6, 9] Although a short period of trial of Tegretol in all patients with facial pain would probably not be harmful, restriction of the use of this drug to classical tic douloureux of spontaneous origin is urged if only to avoid another disappointment in a sufferer whose clinical course is often featured by many previous therapeutic failures.

An additional observation hopefully to be of great benefit if confirmed is the effect of Tegretol in the thalamic syndrome. In the very few patients described in table 1 the immediacy of response in terms of pain relief was just as prompt as it was in trigeminal neuralgia. This was not the experience of another investigator with one "thalamic" patient.[4] However, I believe that the syndrome calls for Tegretol as the primary medication. One patient, H. G., has had to discontinue the drug because of toxicity; remarkably small doses (50 mg. every 2 days) were effective in control of pain, however, and it is hoped that treatment may be resumed soon. Another thalamic patient, case no. 21, L. B., continues to take other medications in addition to Tegretol but in much reduced dosage.

TABLE 1: Effect of Tegretol (Carbamazepine) on Trigeminal Neuralgia, Other Varieties of Facial Pain, and the Thalamic Syndrome

Patient	Age	Disease	Duration	Previous Surgery, Injection	Daily mg. Dosage	Results	Follow-up	Side-effects
1. A. W. H.	WM, 81	Tic douloureux	30 yrs.	+	400	Excellent—no pain	6 mos.*	0
2. F. J. H.	WM, 82	Tic d.	10 yrs.	+	400	Excellent	7 mos.	0
3. C. A. B.	WM, 72	Tic d.	4 yrs.	0	400	Excellent	3 mos.	0
4. D. R.	WF, 66	Tic d.	15 yrs.	+	400	Excellent	5 mos.	0
5. E. W. M.	WF, 70	Tic d.	3 yrs.	0	400	Excellent	4 mos.	0
6. E. L.	WF, 60	Tic d.	3 yrs.	+	400	Excellent	3 mos.	0
7. J. R. T.	WM, 57	Tic d.	6 yrs.	+	400	Excellent	3 mos.	0
8. R. Z.	WF, 76	Tic d. bilateral	6 yrs.	+	2–400	Excellent	4 mos.	0
9. P. G.	WM, 60	Tic d.	3 yrs.	+	400	Excellent	2 mos.	0
10. L. D.	WF, 60	Tic d.	5 yrs.	+	400	Excellent	6 mos.	0
11. E. L.	WF, 77	Tic d.	5 yrs.	+	400	Excellent	2 mos.	0
12. C. Z.	WM, 70	Tic d.	4 yrs.	0	400	Excellent	2 mos.	Severe nausea
13. G. G.	WM, 20	Tic d.	3 mos.	0	400	Good	2 mos.	0
14. A. J. G.	WF, 72	Tic d.	2 yrs.	+	400	Excellent	2 mos.	Temporary fever
15. E. S.	WM, 33	Traumatic supraorbital neuralgia	6 mos.	0	400	Excellent	4 mos.	0
16. E. B.	WF, 72	Postsurgical paresthesias	16 yrs.	+	400	Poor	2 mos.	0
17. L. McK.	WF, 48	Multiple sclerosis with tic d.	5 yrs.	0	400–800	Poor	6 wks.†	0
18. S. F.	WF, 43	Postherpetic facial neuralgia	3 mos.	0	400–800	Poor	2 mos.	0
19. L. D.	WF, 50	Atypical facial neuralgia	4 yrs.	+	400–800	Poor	1 mo.	0
20. V. F.	WM, 34	Atypical facial neuralgia	3 yrs.	0	400–600	Poor	6 wks.	0
21. L. B.	WM, 58	Thalamic syndrome	8 yrs.	0	400	Excellent	2 mos.	0
22. H. G.	WF, 65	Thalamic syndrome	4 yrs.	0	100–400	Excellent	2 mos.	Severe nausea
23. A. K.	WM, 70	Thalamic syndrome	2 yrs.	0	400	Excellent	3 mos.	0

* Alcohol injection performed because of temporary lack of availability of medication.

† Alcohol injection of mental foramen stopped tic pain completely.

Discussion

Explanation of the success of Tegretol in relief of the pain of trigeminal neuralgia necessitates a reëxamination of the tantalizingly baffling etiology of this condition to begin with. Observation of the disease as it occurs spontaneously and of its response to various forms of surgical or other destruction treatment can be summarized thus: Trigeminal neuralgia or tic douloureux occurs almost exclusively in patients 60 years of age or over although an occasional exception may be seen. I have operated on a girl of 19 with classical tic, for example. Trigeminal neuralgia is distinguished from other forms of facial pain, neuralgia or neuropathy by its characteristic of lancinating, stabbing paroxysms of short duration set off by mechanical stimulation of trigger zones in one of the 3 divisional areas of the face and head supplied by the trigeminal nerve. By contrast, atypical facial neuralgia ("Horton's headache," buccal neuralgia, vidian neuralgia, Sluder's neuralgia, carotidynia, etc.) is described by the patient as a steady, boring, grinding, drawing pain beginning in or near the root of the nose, eye, socket of the eye, or forehead, frequently starting in the early morning hours, not lancinating, with no periods of relief in between attacks of pain, associated with feelings of depression and even of suicide. These conditions must not be confused, particularly with reference to the type of treatment to be employed in each.

Trigeminal neuralgia is characterized by periods of spontaneous remission and exacerbations, the former becoming shorter and less frequent as time goes on. Excesses of heat, cold or humidity tend to generate bouts of pain. Inhalation or ingestion of chemicals toxic to the nerve will cause cessation of pain temporarily. Injection of destructive substances (alcohol, formalin) or surgical removal of peripheral branches of the main nerve will eliminate attacks, apparently as a result of the prevention of physiologic afferent impulses from being received centrally to activate a pathologic central mechanism. When nerve branches complete regeneration, attacks begin again. Any type of mechanical trauma (crushing, compression, decompression) to the sensory root of the trigeminal ganglion connecting to the pons will cause cessation of pain for long periods of time but with eventual recurrence in the majority of patients so treated. Permanent relief on the side of the face affected is obtained surgically only by cutting the fibers of the sensory root of the trigeminal ganglion, which do not regenerate, by section of the nucleus of the descending root of the trigeminal nerve in the medulla or by coagulation of the quintothalamic tract in the midbrain. The only medications not directly toxic to the trigeminal nerve or its ganglion prior to the introduction of Tegretol which have been shown to have any beneficial effect are Dilantin (diphenylhydantoin) and Tolseram (mephenesin carbamate).

Although controversy has been severe and opponents sharply divided as to alleged pathologic findings in patients suffering from this unusual disease, it appears that there are no consistent evidences of specific physical damage to neurons or tracts involving the trigeminal projection in the medulla, pons, thalamus, or thalamocortical radiation. There is likewise no real evidence of circulatory disturbances in the domain of the vertebral artery or trigeminal ganglion proper which are causing paroxysmal pain in the face. Turning toward the periphery is reasonable in looking for causation because of the existence of cutaneous trigger zones and the effectiveness of peripheral alcohol block or neurectomy in relieving neuralgia. In one series of cases perifilamentous adhesive fibrotic changes were said to be present around nerve fibers in sections of skin excised from trigger zones.[15] Although most reports state that no abnormalities are seen in portions of excised posterior nerve root during routine pathologic examination, electronic microscopy is said to disclose all types of histologic changes in biopsy specimens taken from the gasserian ganglion of neuralgic patients.[16] How it can be ascertained that such changes are not due to the trauma of surgical removal of nerve tissue is not explained by these investigators. Another etiologic explanation for tic pain, far-fetched at first consideration but possibly meriting closer scrutiny, suggests the disturbance of a virus-host relationship, noting the frequency of the occurrence of herpes simplex labialis or facialis in a high percentage of patients after surgery has been performed on the trigeminal ganglion. It has also been observed that herpes simplex eruption has been seen to precede the development of classical tic pain in the same trigeminal dermatome.[17]

The most complete and one would think the soundest explanation of the rationale of trigeminal neuralgia runs thus: The absence of consistent pathologic changes suggests that the problem is neurophysiologic rather than neuropathologic in nature. Since triggering a susceptible zone in one dermatome of the face sets off pain in another dermatome, the pain mechanism in trigeminal neuralgia must be located centrally. The setting off of pain following stimulation of a trigger involves a certain period of summation latency, is followed by a convulsive type of evoked discharge (lancinating pain) with after-discharge persisting long after stimulation of the trigger has subsided, and with a refractory period following this. The response is too discrete in location to bespeak a cortical or thalamic instigation, indicating that the critical area must lie somewhere between the gasserian ganglion and the thalamus, probably in the lower brainstem. Therefore, trigeminal neuralgia amounts to a pathologic multineuron reflex, involving reverberating circuits extending from the nucleus to the periphery and back again, self-excitatory and featured by after-discharge.[18] It is of further interest to note that the adequate stimulus of eliciting an attack in a period of susceptibility is distortion of hair, skin, and mucosa, bespeaking the participation of fine touch-receptors, since electrical stimulation of trigger zones which would involve large touch organs is not effective in causing pain during a period of susceptibility.[19]

It would appear therefore that the beneficial effect of Tegretol must be exerted upon the trigeminal ganglion and/or its central connections in pathways in the medulla, pons, and quintothalamic projection. Experience with case no. 15 affords a unique opportunity to point out the peripheral-damping effect of the drug. This patient suffered from lancinating supraorbital pains, the definite and exclusive result of direct trauma to the first division of the trigeminal nerve in the orbit. A screwdriver had been driven through the eye, destroying the optic nerve, causing numbness in the forehead and eye, and resulting in the painful syndrome. The very first dose of Tegretol stopped pain completely, and only a small amount of medication was necessary intermittently thereafter. Others have remarked upon the probable action of Tegretol at the first or peripheral primary neuron and in addition at the second or bulbar stage.[4] In summary, it would seem that Tegretol blocks the impulses running from the periphery to the nucleus at the first neuron and that at the medullary level it interferes with impulses radiating toward the reticular polysynaptic system, which is the cause of persistence of the paroxysm due to the reverberating circuits that discharge by converging on the neuron of the nucleus.

Experience with allied painful conditions of the head and neck indicates that Tegretol is not effective in postherpetic neuralgia, atypical facial neuralgia or of any of its variants, "psychalgia," pain due to cervical arthritis, or cervical neuralgia. It is, however, as effective in the very rare glossopharyngeal neuralgia, identical with tic douloureux in everything but location.[20] The effect of Tegretol upon neuralgias elsewhere in the body of whatever cause has been inconsistent and in general has not been found to be favorable, but there is, of course, no reason not to try the drug, especially if pain is suspected of being "causalgic."

It seems almost disloyal for neurosurgeons to sponsor and advocate a medicament for treatment of a disease condition long considered to be the exclusive property of the neurosurgical province. However, a primary principle of ethical conservative surgery is that operative procedures are to be undertaken only when medical treatment is a certainly predictable failure or has proven to be ineffective on trial. Moreover, in the small group of patients (5 to 10 per cent in various surgical series reported) who complain of unpleasant dysesthesias or of numbness in the face after denervating procedures the volubility of reportage of dissatisfaction can be as great, qualitatively and quantitatively, as was the complaint of pain prior to operation. Lastly, the susceptibility of the elderly patient, and tic douloureux is a condition of age, to complications chiefly vascular in association with major surgery must be recalled, even though neurosurgical experience with the tolerance of any type of surgical intervention in this group of patients has been a remarkably happy one.

Turning to the small series of "thalamic" patients treated with Tegretol, cases nos. 21 and 23 were most impressive in relief of that burning, dysesthetic pain usually primary in the face and arm which sometimes comes on after a hemiplegic accident, particularly when the left side of the body is paralyzed. The cause of this type of painful stroke is occlusion of the thalamogeniculate artery which perforates and supplies the very posterior limb of the internal capsule, the sensory thalamus, and the upper mesencephalon. Infarction is believed to result in hyperpathia owing to release from control of the posterior lateral thalamic nuclei and short-circuiting of impulses from phylogenetically old nuclei to the cortex and hypothalamus.[21] Recent depth-electrode studies of such a patient have disclosed what was considered to be an epileptiform focus in the midbrain.[22] "Thalamic" pain in this particular person took its onset in the trigeminal area so that similarity to spontaneous tic douloureux may be said to have been close in every regard.

Summary

Personal experiences with the use of Tegretol (carbamazepine) in the treatment of a variety of painful states involving the head and face are added to the growing world literature which concerns this fascinating new drug. It is apparent that Tegretol can be relied upon to control true trigeminal neuralgia (tic douloureux) and true glossopharyngeal neuralgia. It is not to be considered as effective in atypical facial neuralgias of whatever type, in postherpetic neuralgias of the face, trigeminal neuralgia due to multiple sclerosis, or cervical arthritic neuralgia.

It is my distinct impression that Tegretol is also successful in relieving the pain of thalamic hyperpathia and that it should be used as the drug of choice in the treatment of this agonizingly disturbing syndrome, although the assistance of other medications may be required.

Low doses (200–400 mg. per day) of Tegretol are advised in the management of trigeminal neuralgia. This level is usually effective, and toxicity may be kept to a minimum. If true tic pain persists, the medication may be increased to as much as 800 mg. per day, at least temporarily, or Dilantin (diphenylhydantoin) or ordinary analgesics may be added. As is true of any anticonvulsant or pain-relieving medication, the possibility of rare idiosyncratic reactions involving the bone marrow, skin or other organs must be kept in mind and watched for.

The long history of the disease, tic douloureux, has been featured by repeated introductions of many preparations predicted to be magically curative which have proven to be worthless in the long run. Although the necessity for cautious optimism is thus bespoken, it does indeed seem that now at long last in Tegretol a drug has been introduced which is so specific as to make the primary treatment of trigeminal neuralgia medical, with surgery to be reserved for those patients refractory to medication or intolerably toxic from it. The possibility of placebo effect has been eliminated in a careful study recently reported.[11]

It is to be hoped that Tegretol (carbamazepine) will soon be approved by the Food and Drug Administration so that it will become readily available in this country by medical prescription.

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Echoencephalography—Gokalp, Jakoby and Watts

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of patients with cerebral masses were falsely interpreted as negative and only 1 recording was falsely positive. The number of false negatives can be greatly reduced by recognition of "borderline abnormal" tracings.

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Typhoid Fever: An Historical Sketch

FRANK N. MILLER, M.D.*

Biography of the Disease

ALTHOUGH it doubtlessly existed for centuries previously, the first full description of typhoid fever was that of Thomas Willis in England in 1643 during an epidemic among the Parliamentary troops. The intestinal lesions were first described in 1826 by Pierre Bretonneau, who named the disease dothienenteritis because he considered it an abscess of the small intestine. He believed the ulcers were specific for typhoid fever and differentiated them from tuberculous ulcers. In 1829 Pierre Louis named the disease *fièvre typhoïde*. His student, the American physician William Gerhard, clearly differentiated typhoid fever from typhus for the first time during an epidemic in Philadelphia in 1836, stating that "The anatomical characters of these varieties of fever are peculiar to themselves, and it is as impossible to substitute the lesions of the follicles of the small intestine observed in the typhoid fever for the pathological phenomena of typhus, as it is by treatment or other means to transform the eruption of measles into the pustules of small pox."[1] Ten years later Johann Schönlein distinguished the 2 diseases as typhus exanthematicus and typhus abdominalis. The names of both derive from the Greek *typhos*, meaning smoky or hazy, because of the stupor and delirium which are common in them.

Some opposition to the separation of typhoid fever from typhus persisted for a number of years, but the new concept was fairly generally accepted. To decrease the possibility of confusion between the 2 diseases the American physician, George Wood, suggested in 1847 that typhoid be called enteric fever. William Budd recognized in 1856 that human feces were responsible for transmission, and he proposed the name intestinal fever for the disease. Then in 1880 Karl Joseph Eberth discovered the causative organism, *Salmonella* (Eberthella) *typhosa*, in mesenteric lymph nodes and spleen. Four years later Georg Gaffky grew the organisms in pure culture, and Elie Metchnikoff and Alexandre Besredka infected anthropoid apes in 1900. Meanwhile in 1896 Fernand Widal had discovered the diagnostic agglutination reaction.

As early as 1888 André Chantemesse had investigated the possibility of a typhoid vaccine, and independently Emil Pfeiffer in Germany and Almroth Edward Wright, better known for his blood stain, in England injected dead bacilli as a vaccine in 1894. Within 10 years the prophylactic value of typhoid vaccine was established. By 1908 Major (later Brigadier General) Frederick Russell, who was to become Professor of Pathology and Bacteriology at The George Washington University School of Medicine, developed the typhoid vaccine used by the United States Army. This vaccine was responsible for a great decrease in the incidence of typhoid fever among American troops in World War I as compared to the Spanish-American War and the Civil War. Colonel Joseph F. Siler also contributed to the development of this vaccine.

Typhoid fever had no doubt been a major problem among field troops long before the disease was adequately recognized and diagnosed. Even during the American Civil War there was much confusion in differentiating typhoid fever from the other "continued fevers." It was reported that there were more than 75,000 cases of typhoid fever with about 27,000 deaths among the white troops of the Union Army and 4,100 cases with 2,300 deaths among the Negro troops. There were also about 57,000 cases of typhomalarial fever with more than 5,000 deaths in the Union Army. Mortality was especially high among prisoners of war. About 2,500 cases of tyhpoid fever were diagnosed among Confederate prisoners of war with a death rate of about 50 per cent. Following is a typical case history, complete with pre-chloramphenicol therapy, from the archives of the Civil War:

> "Private F. P. S., Co., 9th Pa.; age 24; had suffered from fever and ague in June 1861; but since then had done his duty uninterruptedly until September 18,

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when he was admitted as a case of typhoid fever. In the evening the patient was weak and had headaches; the bowels were quiet, but there was some tenderness in the right iliac region and intestinal gurgling; face flushed; eyes bright; breath offensive; pulse 88, skin hot and moist; head cool and sweating; tongue grayish-yellow in the centre, red and clean at the edges. Ten grains of calomel and jalap were given. Next day, with a continuance of the symptoms stated, the patient became dull and stupid and had muscae and tinnitus. On the night of the 21st there was delirium and the characteristic (rose) eruption appeared on the 22nd, on which day also he had 2 stools with some tympanites and tenderness; his tongue was black at the base, reddish-white in the centre and red at the tip. Turpentine emulsion and wine were given. Next night he was again delirious, and on the 23rd dull, the skin unaltered save by the fading of the eruption from the chest and abdomen, the bowels quiet, slightly tympanitic but free from tenderness. Dover's powder was given in small doses, with stimulants. An enema was administered on the 24th, with 2 grains of blue-pill and 1 of quinine every 3 hours. By the 26th the eruptions had disappeared, but the patient continued dull; the skin was moist, the tongue cleaning. The bowels were moved once on this day and on the 27th; . . . but after this the tongue became clean, the appetite good and the bowels natural. The patient was returned to duty October 20."[2]

The control of typhoid fever is mainly a public health problem. This concept is strikingly presented in *An Enemy of the People*, written by the Norwegian dramatist, Henrik Ibsen, in 1882, only 2 years after the discovery of the causative organism of typhoid fever. However, Ibsen does not seem to have been aware of Eberth's recent achievement, as is indicated in the following extract from Act I:

> Dr. Tomas Stockmann: . . . Well—do you know what these Baths are? These precious, magnificent Baths that have been established at such great expense—can you guess what they really are?
>
> Hovsted: No—what? . . .
>
> Dr. Stockmann: They're nothing but a pest hole! . . . The whole institution is a whited sepulcher, spreading poison; it's a menace to the Public Health! . . . I've made the most painstaking investigations. I'd suspected something of the sort for quite some time, you see. I was struck by the curious amount of illness among the visitors at the Baths last year—there were several cases of typhoid and gastric fever—
>
> Mrs. Katrine Stockmann: Yes, I remember.
>
> Dr. Stockmann: At first we took it for granted that the visitors brought the infection with them; but later —this past winter—I began to think differently. I set to work to analyze the water, as best I could—
>
> Mrs. Stockmann: So that's what you've been working at!
>
> Dr. Stockmann: Yes—I've worked very hard at it, Katrine, but I didn't have the necessary equipment here; so I finally sent samples of the drinking water and the sea-water by the beach to the laboratories at the university, and asked them to give me a full analysis.
>
> Hovsted: And is that what you have just received?
>
> Dr. Stockmann (showing the letter): Yes—here it is! It proves beyond the shadow of a doubt the presence of decayed animal matter in the water—millions of Infusoria. The use of this water, both internally and externally, is in the highest degree dangerous to health.[3]

Although Dr. Stockmann was defeated in his efforts by vested interests and public ignorance, dedicated men like him persevered. The public health menace of typhoid fever has been met magnificently in the United States. By means of vaccination, modern sewage disposal, water purification, pasteurization of milk, and the control of carriers, the disease is today uncommon. Only 859 cases with 22 deaths were reported in the United States in 1959 as compared with about 350,000 with 35,000 deaths in 1900. This reduction in incidence has been a remarkable feat, but it can be maintained only by constant vigilance over the purity of our water and food supplies, lest this classic disease with its protean manifestations shall become more prevalent among us. As has been pointed out by an apt quotation from Shakespeare's *Macbeth*, "We have scotch'd the snake, not kill'd it."[4]

The Disease in a Biography (Franz Peter Schubert)

When Franz Schubert succumbed to typhoid fever at the age of 31 the world of music suffered one of its most terrible losses. The career of Schubert in many respects parallels that of John Keats who died in his twenties of tuberculosis. Like Keats, Schubert was a lyricist, the greatest melodist who has ever expressed himself in music. Again, like the English poet, Schubert had only a few years of maturity. About 3 years before his death Schubert's music took on a new seriousness and depth of expression, and once more, like Keats, he had a final year in which he produced a tremendous volume of work of the highest quality and of almost unsurpassed beauty. Then at 31, having reached the height of his powers, Schubert suffered an acute illness, and the glorious flood of singing melody was dammed up forever.

Franz Schubert, the son of a schoolmaster and a cook, gave forth his first most unmusical cries near Vienna, Austria on January 31, 1797. The boy was precocious and began his musical instruction at the age of 5. When he was 11 he was given a scholarship to the Konvikt, the leading music school in Vienna. Here his training was mainly vocal, and he remained at the school until 1813, when his voice changed. Meanwhile his mother had died of typhoid fever in 1812. Schubert's first musical composition, a fantasia for piano, was written at the age of 13. From 1812 to 1816 he composed chamber music for home performances. His first symphony, in D major, was written at the age of 16. The year 1814 brought forth about 150 songs, including the famous setting of Goethe's *Gretchen at the Spinning Wheel* (figure 1). For 3 years, in order to escape military service, Schubert taught in his father's school. In late 1816 he left his father's school and began the Bohemian existence which he lived until his death. His obvious talents, shown even in his early music, brought him many admirers among the poets and artists of Vienna. He became the center of a cultural group, and evenings of his music became known as Schubertiaden. Having no money of his own, he was supported by his fellow musicians and artists.

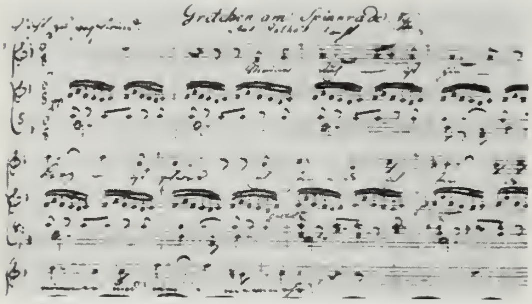

FIG. 1. Manuscript of Schubert's song, Gretchen at the Spinning Wheel.

In the autumn of 1822 Schubert contracted syphilis. He suffered severe secondary lesions with a rash that covered his entire body. His hair had to be cut off because of a scalp rash, and he wore a wig for much of the following year. The lesions recurred several times and caused Schubert great despair and shame. In May 1823 he spent a week in the Vienna General Hospital. Shortly thereafter he wrote to a friend, "I almost begin to doubt whether I shall ever be completely well again." Then in late November his "health, . . . thank God, seems to have recovered," and in December a letter stated that "Schubert is better, it will not be long before he has his hair again." By February 1824 a friend wrote of him, "Schubert is very well. He has given up his wig and reveals a pretty head of short, curly hair." However, in March 1824 the composer wrote: "I feel myself to be the most unhappy and wretched creature in the world. Imagine a man whose health will never be right again and who, in his despair over this, constantly makes things worse instead of better; imagine a man, I say, whose brightest hopes have come to nothing, to whom the happiness of love and friendship offer nothing but pain, whose enthusiasm (at least the stimulating kind) for beauty threatens to vanish; and then ask yourself if he is not indeed a wretched unhappy creature?" In late 1825 Schubert began to have excruciating headaches, probably due to meningovascular syphilis (figure 2). These headaches continued for the remainder of his life. His spirits bounded between deep depression and exuberant periods during which he was able to compose some of his greatest music.

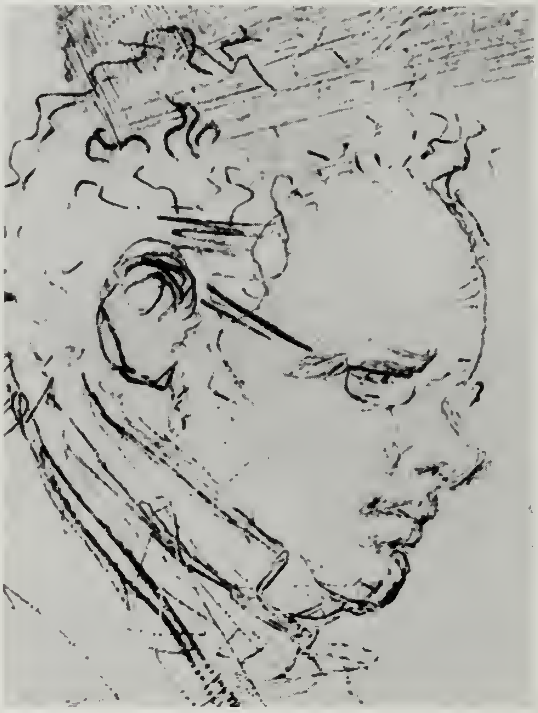

Fig. 2. Pencil sketch of Schubert in 1825.

Even during the prolonged illness Schubert was able to continue composing. In October 1822 he wrote what is perhaps his best known work, the "Unfinished Symphony in B Minor." The mystery of why this work was never completed has not been solved. The most widely accepted theory is that Schubert was never again able to regain the mood in which he had composed the first 2 movements. It has also been held that the symphony was actually finished, the final 2 movements having been lost or transferred by the composer to his incidental music for the play *Rosamunde*. This symphony is not the only incomplete work in Schubert's catalog, for there are many fragmentary compositions, including 2 other symphonies, which are intriguing in their unfinished form.

In October 1827 Schubert entered a year of productivity that can only be compared with the *annus mirabilis* of John Keats. The year began with the composition of Book II of the song cycle, *The Winter Journey*. The songs of this tragic cycle, which seem to have reflected Schubert's mood during this period, have been called "24 of the most profound variations on the theme of man alone in all the arts." There followed a succession of masterpieces sufficient to fill a composer's lifetime. These include the trio in E flat major for piano, violin, and 'cello; the last 4 Impromptus and the Moments Musicaux for piano; the magnificent C major symphony, which is comparable in power and sweep to the greatest symphonies of Beethoven; the Mass in E flat major, Schubert's finest setting of the Catholic ritual; a number of songs which were collected as a cycle entitled by the publisher *Swan Songs* and which included a number of settings of the lyric poems of Heinrich Heine; the poignantly beautiful string quintet in C major; and finally 3 piano sonatas, which except for a few short pieces completed the wonderful year.

On October 31, 1828 Schubert became nauseated while eating some fish in a tavern. He had contracted typhoid fever from the notoriously infected water of his district in Vienna. For the next 2½ weeks he ate almost nothing because of the constant nausea and intestinal disturbance. Ironically, the composer whose natural gifts were almost unparalleled and who had had almost no formal instruction in composition began the study of counterpoint on November 4. However, by November 11 he was bedridden. He had been seen the previous day by Dr. Josef von Vering, a specialist in venereal diseases, and Dr. Johann Wisgrill. On November 12 he wrote to a friend: "I am ill. For 11 days now I have neither eaten nor drunk anything. I totter from the bed to the sofa and vice versa. . . . If I swallow anything I promptly bring it up again." During his illness Schubert read "The Last of the Mohicans" and "The Pilot" by James Fenimore Cooper in German translation. He also corrected the proofs of his song cycle, *The Winter Journey*. On November 17 he became delirious and had to be restrained. Frightened by the darkness of his room, he cried out to his brother who was nursing him, "Why do you let me lie in this black hole?" (figure 3). Two days later Schubert turned toward the wall and quietly said, "Here, here is my end." In the family records his father wrote: "Franz Peter, Wednesday, 19 November 1828, 3'clock in the midafternoon (of typhoid fever), buried Saturday, 22 November 1828."

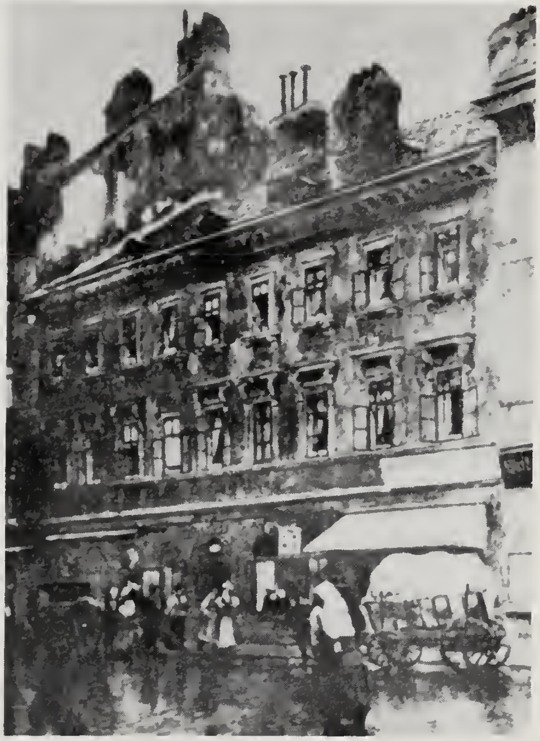

FIG. 3. House in Vienna in which Schubert died.

Besides the untold wealth of unpublished manuscripts, Schubert left an estate of about $20. The medical expenses of his last illness came to about $40. He was buried beside Beethoven, the man whom he revered above all others, in Vienna's Währing cemetery. No truer epitaph was ever carved than that which the poet Franz Grillparzer wrote for Schubert:

> "The art of music here entombed a rich
> possession but even fairer hopes."

Despite his short life, the musical achievement of Schubert is tremendous. He ranks first in the great line of German song composers which includes Robert Schumann, Johannes Brahms, and Hugo Wolf. Schubert composed more than 600 songs, among which are some of the very finest and most penetrating ever written. His piano music has remained underestimated, and a number of his later sonatas are worthy to rank with those of Beethoven. He was the first important composer to write short lyric pieces for the piano, thus setting an example for many later romantic composers. Among his 10 symphonies are 2 of the finest examples of this form. He brought a poetic quality to the symphony which greatly influenced Brahms. Schubert holds a place as one of the most important composers of chamber music, especially for his last 3 string quartets, 2 piano trios, piano quintet, octet and string quintet, which stands at the very pinnacle of his accomplishment. Living under the imposing shadow of Beethoven and deeply admiring his older contemporary, Schubert was still able to avoid the influence of Beethoven. He brought to his music an unmatched lyric sweetness, a charming naïveté and rich harmonic coloring. Franz Liszt called him "the most poetic musician who ever lived," and Johannes Brahms wrote: "Where else is there a genius like his, that soars with such boldness and certainty to the sky where we see the very greatest enthroned? He impresses me as a child of the gods, who plays with Jove's thunder, and occasionally handles it in an unusual manner. For he does play in a region and at a height to which the others can by no means attain."

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Thyroid Analogue for Hypercholesterolemia—Rose, Orvis and Kramer

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Drug Allergy in Tuberculous Patients—Brown, Jennings, Coleman and Bulubash

(Continued from page 657)

The patch test may be helpful in predicting safety or likelihood of recurrence of allergy upon readministration of a culprit drug. Further study is needed to elucidate this and other points.

Acknowledgment: We should like to acknowledge the invaluable services of Mrs. Virginia Earle, R. N., whose devotion and ingenuity made possible the accomplishment of this project.

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A Method of Anesthesia for the Apprehensive Gynecological Patient

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ANESTHESIA for the apprehensive woman scheduled for gynecologic surgery is a continuing problem for the patient, gynecologist and anesthesiologist. Various approaches to this situation have been utilized. The time-honored method involves heavy premedication. This has been associated occasionally with respiratory and circulatory depression.

Rectal anesthesia with tribromethanol in amylene hydrate‡ was introduced in the 1920's. The use of a predetermined fixed dose was sometimes followed by respiratory and circulatory depression. The individual preparation of solutions, administration of anesthetic, and time of anesthetic appearance usually required an additional half hour. This method has been little used since the advent of intravenous barbiturates. In recent years hypnosis has been tried, but it is time-consuming and has very limited acceptance.

Alleviation of fear is one of the ever-present problems in patients who are to have gynecologic surgery. Those fears are centered around the fear of death, the fear of what may be found at the time of the operation, the fear of her status after the removal of a female organ or organs, the fear of being transported through the halls and elevators, and the fear of "going under" an anesthetic.

Many patients have stated that they are more afraid of being given an anesthetic than they are of having the required surgery. Many patients still remember previous ordeals of having had anesthetic masks placed over their faces. That aspect of anesthesia seems to create an indelible impression.

In recent years, through close coöperation of the Departments of Anesthesiology and Gynecology, a method for the alleviation of anesthesia fears has been devised. That method involves primary recognition by the gynecologist of apprehension on the part of the patient. He then explains to the patient that she need have no fear of anesthetics or of seeing the operating room. It is explained to her that she will be put to sleep in her room and that she will not be aware of the actual time the anesthesia is started. This method has been used with increasing frequency and has been of inestimable value in the management of an increasing number of gynecologic patients. It has proved itself to be a most valuable addition to the armamentarium of the gynecologic surgeon.

Thiopental sodium§ induction of anesthesia in the patient's room before surgery has been the method of choice in the George Washington University Hospital for handling this particular problem. We present now a series of 314 cases that have been managed in this manner from January 1962 through May 1965.

Method

Each patient is seen by the anesthesiologist the night before surgery. The hospital record is checked and the patient interviewed. Questions are answered, fears are allayed, and the patient is told she will be asleep before leaving her room. The gynecologist talks to his patient before anesthesia is started on the morning of surgery.

Capsules of pentobarbital sodium‖, 50 or 100 mg., are given the night before surgery and repeated 2 hours before surgery. We do not use parasympathetic depressants or narcotics. Atropine, morphine, and related drugs for routine premedication have not been used since 1950 in the George Washington University Hospital.[1, 2, 3]

We routinely use an operating room stretcher especially equipped with an E cylinder of oxygen. An oxygen gauge is connected to a 5-liter breathing bag and anesthesia mask. A sidearm is connected to a Venturi-type valve connected to a bottle, tubing and catheter for suction purposes

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‡ Trade name: Avertin.®

§ Trade name: Pentothal.®

‖ Trade name: Nembutal.®

(figure 1). These extra supplies cost less than \$100, are readily obtained, and can be added to any stretcher. If this specially equipped stretcher is not available, a regular stretcher is used and a Kreiselman Adult Resuscitator or other mechanical apparatus of this type is utilized for positive-pressure oxygen, straight-flow oxygen, and suction.

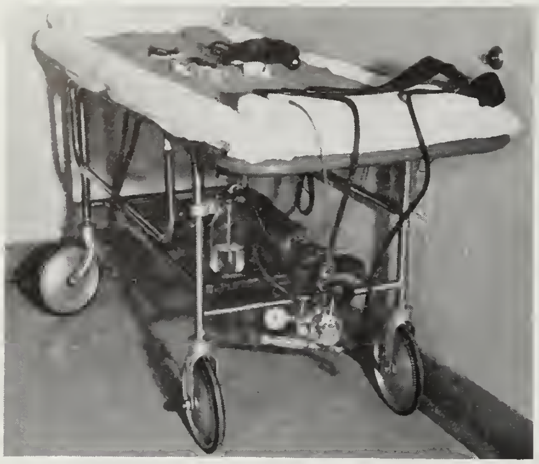

FIG. 1. Operating room stretcher with necessary equipment.

When the operating room is in readiness and the assistants start to scrub, the anesthesiologist proceeds with an operating room orderly to the patient's room. The usual items necessary for the conduct of intravenous anesthesia are placed on the stretcher (figure 2):

Blood pressure cuff and sphygmomanometer
Stethoscope
Oral airway
Thiopental sodium 2½ per cent in a 30 c.c. syringe
3-way stopcock
30 cm. sterile plastic tubing
18- or 20-gauge needles
Tourniquet
Alcohol sponges
Adhesive tape

The anesthesiologist and nurse check the patient's identity and help in the move from the bed to the stretcher. The presence of the patient's special nurse or of the floor nurse is emphasized. This assists in proper identification and insures the presence of another person when the patient is put to sleep and transported to the operating suite. These patients are lightly anesthetized, and the possibility of bizarre dreams with resultant false allegations and malpractice liability must be considered.

The stethoscope and blood pressure cuff are applied and the pre-anesthetic blood pressure reading recorded. The tourniquet is applied to the opposite arm, and the skin overlying a readily accessible vein on the forearm (preferably away from the wrist and elbow) is cleaned with the alcohol sponge. The needle attached to the previously assembled tubing, stopcock and thiopental sodium syringe is inserted, and 2 c.c. (50 mg.) of thiopental sodium is injected as a test dose. After a minute, to judge the patient's response, a sleep dose of thiopental sodium is injected.

The anesthesiologist then rechecks the blood pressure and maintains the patient's airway by elevating the chin, and the patient is promptly taken to the operating room. Supplemental doses of thiopental are given if necessary.

The patient is moved from the stretcher to the operating room table by the draw-sheet already on each stretcher. If a vein in the forearm was not obtainable and one in the wrist or elbow joint was used, it is suggested that an arm board be used to avoid displacing the intravenous needle. Anesthesia is continued in the operating room with one of the inhalation agents.

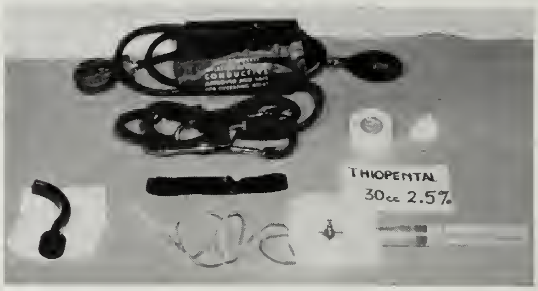

FIG. 2. Items needed for intravenous anesthesia in the patient's room.

Results

The advantages and acceptance of this method by the patient are attested by 306 of the 314 patients in this series (98 per cent), who said they liked this technique and would have it again for future surgery.

The amounts of anesthetic given in the patient's room, the additional amount administered on the way to the operating room, and the total dosage are summarized in table 1.

It is evident that the total dosage of thiopental sodium was kept at a minimum; only 18 patients (5.7 per cent) received over 500 mg.

The time necessary to begin intravenous anesthesia in the patient's room and then transport the patient to surgery is presented in table 2.

The great majority of patients (86 per cent) required from 5 to 10 minutes. It is apparent that little additional time was actually necessary.

TABLE 1: Patients Receiving Thiopental
Dosage and Location of Administration

Thiopental, mg.	In Room		Additional to Operating Room		Total	
	Patients	Per cent	Patients	Per cent	Patients	Per cent
100 or less	33	10.5	176	72.4	14	4.5
125–200	104	33.1	48	19.8	51	16.2
225–300	122	38.9	10	4.1	94	29.9
325–400	42	13.4	5	2.1	106	33.8
425–500	8	2.5	1	.4	31	9.9
Over 500	5	1.6	3	1.2	18	5.7
	314	100.0	243	100.0	314	100.0

The blood pressure is checked preoperatively, after induction, and on arrival in the operating room. Since the anesthesia is not deep, circulatory changes are minimal.

TABLE 2: Time Required for Technique
(from patient's room to operating room)

Minutes	Patients	Per cent
Less than 5	14	4
5–10	269	86
11–15	25	8
Over 15	6	2
	314	100

Oxygen by positive pressure and straight flow is always available in the event of anesthetic overdosage and respiratory or circulatory depression. This was used in 3 cases, an incidence of 1 per cent. No other treatment was necessary.

There were 7 cases in which coughing occurred. Two patients required suction for the removal of secretions, and the others were handled by an additional injection of anesthetic.

There was 1 patient who regurgitated and was managed by the available suction. We are most aware of this ever-present hazard and use this technique only for patients who have been routinely prepared for surgery with no food or drink since the previous night.

Comment

The 314 patients had 4.2 per cent of the 7,449 gynecologic procedures during this period. This technique was used a total of 1,580 times for all types of surgery in that same time interval, and there were no noteworthy complications.

Requests for thiopental induction in the room have been made by patients, surgeons and anesthesiologists, as indicated in table 3.

TABLE 3: Request for Anesthesia in Room in 314 Cases

Requested by	Cases*	Per cent
Patient	130	41
Surgeon	166	53
Anesthesiologist	96	31

* Total is over 100 per cent because of duplication of requests.

Early in the series the use of this method was initiated by the anesthesiologist. Now it is customary for the gynecologist in his office to recognize a patient who is a candidate for this technique and to alert the anesthesiologist when surgery is posted. Patients who have heard of this type of anesthesia from friends are asking for it themselves.

There are few contraindications to this method. It is primarily the good judgment of the anesthesiologist to decide what is an absolute and what a relative contraindication in each individual case. These contraindications are summarized as follows:

1. Recent food intake
2. Respiratory problems with airway interference
3. Severe cardiovascular disease
4. Hiatal hernia with history of regurgitation
5. Difficult venipuncture
6. Contraindication to barbiturates

Those who had previous anesthetics in the operating room were particularly appreciative of this method. Many mentioned the ride on the stretcher, the bothersome operating room spotlights, delays for surgery, hearing conversations of operating room personnel that frightened them, and the dislike of heavy medication.

The disadvantages include the need for extra personnel, special attention to the use of the intravenous needle while moving the patient, and the extra demand on the anesthesiologist's time.

Summary

We have presented a method of anesthesia for the apprehensive gynecologic patient. There have been no serious complications associated with this technique, and it has been enthusiastically received. This method is simple, requires little additional equipment and time, and is pleasant and safe for the patient. This has been shown to be a most satisfactory way to anesthetize the apprehensive gynecologic patient.

(*Continued on page 702*)

Anesthesia Deaths in 156,714 Anesthetics Administered at the George Washington University Hospital, Washington, D. C., 1948–1962

PAULA R. KAISER, M.D.*, AND CHARLES S. COAKLEY, M.D.†

ANESTHESIOLOGISTS AND SURGEONS have been increasingly concerned over the mortality associated with anesthesia and surgery. The apparent increase in mortality has been attributed to many causes. Among these are the increased number of poor-risk patients who undergo surgery, the increasing number of long or complicated surgical procedures, particularly those involving the cardiovascular and neurological systems, and the introduction of new drugs or methods of anesthesia.

However, when looking into individual histories one is impressed by the fact that often the good-risk patient undergoing a routine operation suffers an unexpected fatality. It is very difficult for one physician to gather enough information in his own practice to reach significant conclusions. If enough anesthesiologists would report on large groups of patients the increased body of knowledge would yield information which would be of aid in evaluating this problem and perhaps reduce the serious risks involved in anesthesia.

Literature on this subject was reviewed in order to have some basis of comparison with our results. Table 1 summarizes some of the statistical facts which were obtained.[1-8]

Vincent Collins,[9] in discussing fatalities in the operating room, estimates an overall mortality of 1:1,000 to 1:2,000 operations. Of that, he roughly estimates the incidence of anesthesia-related deaths to be 1 in 3,000 to 1 in 5,000 anesthetics. Also, he thinks that one should limit the term "cardiac arrest" to iatrogenically produced cardiocirculatory collapse rather than have the term include deaths in the operating room from all causes. We believe with him that one might get a much better idea of the true incidence of cardiac arrest if the term was more carefully used.

Method of Study

All 24-hour surgical deaths during the years 1948–1962 inclusive were studied in order to ascertain the number of deaths which were attributable to anesthesia. In this paper "anesthesia death" includes deaths in which anesthesia was either the primary or a contributory factor.

During the years studied, 156,714 anesthetics were administered in the surgical and obstetrical departments of our Hospital. This figure includes all types of surgical procedures including gynecological, urological, orthopedic, neurosurgical, and intrathoracic. All age-groups were involved, from infancy to 99 years. The majority of anesthetics in the Hospital have been administered by residents with supervision from our staff, and the remainder by staff physicians who were either diplomates or eligible for certification by the American Board of Anesthesiology.

This report represents the accumulation of statistics over a 14-year period. In compiling these statistics, reports were studied which were made at the time of death for each 24-hour surgical death and any other surgical death in which anesthesia might have played a role. In addition, the records of all surgical deaths were obtained fron the Medical Records Division of the Hospital and reviewed to find 'anesthesia deaths' which occurred after 24 hours.

The decisions as to the cause of death were made by the anesthesiology staff following consultation with at least 1 surgeon and a pathologist, when either autopsies or tissue examinations

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TABLE 1: Anesthesia Mortality

Source	No. Anesthetics	Date	Deaths	Totals	Primary
Lotz, A. King, Wilmington	32,883	1937	17	1:1,934	—
Waters, R. M., and Gillespie, N. A., University of Wisconsin	44,894	1944	30*	1:1,496	1:3,453
Trent, J. C., and Gaster, E., Duke University	58,128	1944	27†	1:2,004	—
Beecher, H. K., and Todd, D. P., 10 Universities	599,548	1954	384	1:1,560	1:2,680
Jacoby, J. J., Ohio State University	54,000	1955	5	1:10,800	1:27,000
Phillips, D. C., et al., Baltimore	490,000	1960	196	1:2,500	1:7,656
Dripps, R. D., et al., University of Pennsylvania	120,000	1961	80	1:1,500	1:3,076
Clifton, B. S., and Hotten, W. I. T., Royal Prince Alfred Hospital	205,640	1963	52	1:3,954	1:6,048
Kaiser, P. R., and Coakley, C. S., George Washington University	156,714	1966‡	18	1:8,706	1:39,178

* Deaths in operating room.

† Sudden deaths during and directly after surgery.

‡ To be published.

TABLE 2: Anesthetic Deaths*

Year	Total Anesthetics	Anesthesia Primary	Anesthesia Contributory
1948	4,538	0	0
1949	8,129	0	0
1950	9,367	0	1
1951	9,630	0	0
1952	9,932	0	3
1953	10,643	0	2
1954	10,865	0	0
1955	11,384	0	0
1956	11,294	3	0
1957	12,112	0	0
1958	12,007	0	3
1959	11,702	0	1
1960	12,096	0	2
1961	11,837	1	2
1962	11,776	0	0
Totals	156,714	4	14

* Total anesthetic deaths 18.

were available. In recent years an even closer liaison has existed between the surgical and anesthesiology departments. Joint mortality conferences are held each month at which all surgical deaths are discussed. Admittedly, it is sometimes difficult to assign a definite cause of death, but in this paper anesthesia was incriminated even when there was considerable doubt.

Results

The number of anesthetics administered and the number of deaths which were related to anesthesia are shown in table 2. There was a total of 18 anesthesia deaths in 156,714 anesthetics, an incidence of 1:8,706. In 14 cases anesthesia was regarded as contributory. In 4 cases anesthesia was considered the primary cause, giving an incidence of 1:39,178.

The histories of the patients whose deaths were anesthesia-related were studied in an attempt to find some common factors which may have accounted for their inability to withstand the stress of operation and anesthesia. The following factors were considered to be pertinent:

I. *Age*—12 patients were over 50

II. *Physical status**—14 patients were in poor condition

Physical Status	No. Patients
1	1
2	2
3	9
4	2
5	1
6	3
7	0

III. *Preoperative preparation*

	No. Cases
1. Inadequate preoperative evaluation of the cardiac status of a 28-year-old hypertensive female	1
2. Poor preoperative management of an obstructed airway (preoperative tracheostomy advisable)	1
3. Poor surgical preparation (uncorrected preoperative electrolyte imbalance)	1

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* Physical Status according to ASA prior to 1962: Grade 1. An individual with no organic disease or with localized disease which causes no systemic disturbance; 2. An individual with moderate systemic disturbance; 3. An individual with severe systemic disturbance; 4. An individual suffering from systemic disorders which are an imminent threat to life; 5. Emergency conditions which would otherwise be in Grade 1 or 2; 6. Emergency conditions which would otherwise be in Grade 3 or 4; 7. All patients who are moribund.

IV. *Anesthetic management*

A. Contributory causes:

	No. Patients
1. Hypoxia during 2 attempts at intubation, delayed resuscitation, coronary thrombosis in a hypertensive patient with cardiovascular disease	1
2. Hypotension following premedication, uncorrected $1\frac{1}{2}$ hours in a patient with hypertensive cardiovascular disease	1
3. Cardiac arrest following 5 minutes of Vinethene® ether in a patient with undiagnosed congenital heart disease	1
4. Cardiac arrest and death following 10 minutes of Pentothal®, nitrous oxide and Flaxedil® and ether in a patient with severe hypertensive cardiovascular disease	1
5. Induced hypotensive technique (Pendiomid®) for surgery on a 62-year-old woman for hemangioma of the brain	1
6. Repeated hypotension resulting in a massive coronary occlusion after 5 hours and 15 minutes of anesthesia	1
7. Hypotension repeated during surgery in a cardiac patient (mitral and aortic disease)	1
8. Cardiac arrest following 75 mg. of Pentothal in a patient with rheumatic heart disease	1
9. Hypotension in a cardiac patient with electrolyte imbalance	1
10. Difficult intubation, too much surgery and anesthesia in a poor-risk patient (previous neck dissection, metastatic carcinoma, myocardial ischemia—preoperative tracheostomy advisable)	1
11. Cardiac arrest following 6 hours of anesthesia and hypothermia in a poor-risk patient with severe coronary artery disease	1

B. Primary causes:

	No. Patients
1. Hypotension due to combined caudal and general anesthesia	1
2. Cardiac arrest following unrecognized asphyxia due to a poor airway	2
3. Postoperative obstruction in an unreacted patient	1

Discussion

Available anesthesia mortality figures indicate that better techniques and drugs to reduce the incidence of deaths from anesthesia are indicated.

Though a large number of deaths occurred in the older age group, it was not thought that age is the important factor since most of the older patients were also in the poor-risk group. Since the patient's preoperative disease was an important factor in a large number of deaths, a very careful preoperative evaluation of the patient is essential, and, whenever feasible, attempts should be made to correct any reversible condition. This involves teamwork among the surgeon, physician and the anesthesiologist. The use of a tracheotomy preoperatively may have saved the life of one of the patients. A careful investigation of the cardiac status of a young hypertensive patient may have prevented the catastrophe in her case.

During anesthesia a slow, careful induction is of great importance, particularly in the poor-risk, elderly patient. The avoidance of asphyxia, careful attention to airway maintenance, and correction of hypotension, protracted or repeated, would seem to be vital precautions both in the prevention of cardiac arrests and the other less dramatic fatalities.

There were no changes in anesthetic methods during the last 7 years to account for an increase in cardiac arrests (table 3). The only difference noted was an increase in the use of relaxants, though in no case did the use of relaxants cause the death. However, it would seem apparent that the use of muscle relaxants makes it even more necessary to devote strict attention to ven-

TABLE 3: Cardiac Arrests in the Operating Room

Year	Arrests	Massage*			Resuscitated	Died
		(a)	(b)	(c)		
1948	0					
1949	0					
1950	0					
1951	0					
1952	2	2	0	0	1 (3 hrs.)	2 (a)
1953	1	1	0	0	1 (a)	0
1954	1	1	0	0	1 (a)	0
1955	0					
1956	2	2	0	0	1 (11 hrs.)	2 (a)
1957	1	0	0	0	1 (4 days)	1
1958	4	0	1	2	2 (1b, 1c)	2
1959	1	0	0	1	1 (58 hrs.)	1 (c)
1960	2	1	0	1	1 (c)	1 (a)
1961	4	0	2	2	2 (1b, 1c)	2 (1b, 1c)
1962	4	0	4	0	4 (b)	0
Totals...	22	7	7	6	11*	11

* (a) Thoracotomy—cardiac massage; (b) closed chest cardiac massage; (c) closed chest cardiac massage and thoracotomy.

tilation. Inadequate respiratory exchange must be corrected either by assisted or controlled respiration.

At the George Washington University Hospital controlled respiration is rarely used. In the majority of cases, ventilation is assisted manually.* We believe the persistence of spontaneous respiration is an important safety factor. This practice may have substantially contributed to the lower anesthesia mortality in this institution.

Attention to the anesthetized patient should be constant while he is in the operating room and until he is fully reacted. The use of a well-equipped, well-staffed recovery room has done much to improve postoperative care. One fatality involved an infected patient who bypassed our recovery room because of the necessity that he be isolated and he was left unattended. The arrest, which apparently occurred following asphyxia from respiratory obstruction, was discovered but resuscitative measures were instituted too late. This case emphasized the importance of constant supervision of unreacted patients. Our new recovery suite has provision for isolation patients.

A prompt resuscitative routine is vital. In 2 cases of delayed resuscitation 1 was due to unrecognized prolonged asphyxia. The other occurred in an area removed from the main operating room where efforts at ineffectual external resuscitation were carried on too long before internal massage was performed.

Stephen[10] reported in 1962 on 164 cardiac standstills which occurred in Duke University Hospital during the years 1950–1959 in 118,552 patients. The total incidence of anesthesia-related standstills was 1:1,669 with a mortality incidence of 1:1,975. They also reported that in 1950 the anesthesia-related standstills were 1:1,062. In 1959 the anesthesia-related standstills had decreased to 1:3,884.

In the George Washington University Hospital during the years 1948–1962, 22 cardiac arrests occurred in the operating room in 156,714 patients, of whom 50 per cent were successfully resuscitated. The total incidence of cardiac arrest was 1:7,123, and the mortality incidence was 1:14,428. Of these 22 arrests 11 were considered to be anesthesia-related; 8 of these patients died, giving a mortality incidence of anesthesia-related arrests of 1:19,589.

We agree with many of our colleagues that prompt resuscitation can save lives. It is the responsibility of surgeons and anesthesiologists to be on the constant alert. It is not within the scope of this paper to discuss specific monitoring devices. Whatever is needed to monitor a patient's general condition and his vital signs carefully should be utilized. In the past few years we have increased the number of cardioscopes in our operating and recovery rooms. They are used for all poor-risk patients and during major surgery. A central monitoring room is available in which all oscilloscopic tracings may be observed and recorded by a technician or consultant. The oscilloscopic tracings in the operating rooms are regularly observed by the anesthesiologist. Pulse monitors, venous and arterial pressures may also be monitored as indicated.

Above all, an alert anesthesiologist should be at the "head of the table" and must constantly use all of his 5 senses.

We join Dripps[7] in his plea for detailed written death reports on all deaths occurring within 24 hours of surgery. In addition, reports should be made on all other deaths in which anesthesia may be a factor. It is hoped that more anesthesiologists will combine to form anesthesia study commissions along the lines of the Baltimore Study Commission. In the Washington area such a group has recently been formed. By constant study of mortality and morbidity, information will be gained which will help to prevent catastrophies.

Summary

This has been a report on the anesthesia deaths which occurred during the years 1948–1962 in the George Washington University Hospital. In 156,714 anesthetics there were 18 anesthesia-related deaths, giving an incidence of 1:8,706, and 4 primary anesthesia deaths, giving an incidence of 1:39,178.

Important factors causing anesthesia deaths were found to be inadequate preoperative evaluation or preparation of patients and hypoxia, asphyxia, and/or hypotension during the conduct of the anesthesia.

Recommendations have been made regarding methods of improving the care and monitoring of patients. We also urge that area study groups be formed to collate and evaluate all available data on anesthesia morbidity and mortality.

(*Continued on page 702*)

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* In recent years the only exception has been in craniotomies in which a mechanical ventilator has been used to produce positive and negative pressure to reduce brain volume.

PRESIDENT'S PAGE

A PROGRESS REPORT

Since I am concluding my year as President of the Medical Society of the District of Columbia this month I would be remiss if I failed to express my sincere gratitude and thanks to the many members of the Society and its staff for their helpful coöperation and support during my tenure. It has been a rewarding and instructive experience, leaving me with a tremendous respect for the many hands that collectively make our Society one of the best in the country.

Early in the past year the transition from our old to our new headquarters was made with a minimum of interruption in the affairs of the Society. With the increased activities associated with our newer and larger building, the increased demands on the staff of the Society were admirably handled; however, continued increase in the use of our headquarters has created an obvious need for enlargement of the staff.

During the year the inauguration of Medicare took place in a quiet and orderly fashion; the coöperation of our local medical community was largely responsible for this. The Society through its representation on the various subcommittees of the Health Department has played an effective role in the design of Medicaid, the implementation of Title XIX of Public Law 89–97. Our Society has spearheaded the development of a Planning Grant for the Development of Regional Centers for Heart, Cancer and Stroke in the District of Columbia. This application has already received approval from the National Institutes of Health and is being put into operation immediately. The system of medical licensure in the District of Columbia is being surveyed by a committee of the Society whose recommendations will be soon forthcoming. Insurance programs for the total membership of the Society including the group life insurance and the improved tax-free pension program relating to the Keogh Bill have been developed and are being presented to the membership. These accomplishments during the past 12 months are the basis for considerable satisfaction.

It is my firm belief that during the term of my capable successor, Dr. Henry D. Ecker, continued and more significant progress will be made.

Robert J. Coffey

SQUIBB NOTES ON THERAPY

"'Tranquilizer' is not a good word"[1]

"THIS classification is psychologically too seductive, pharmacologically too unspecific, and in terms of results not infrequently untrue."[2]

What is a tranquilizer? According to the 24th Edition of Dorland's Medical Dictionary[3] a tranquilizer is "an agent which acts on the emotional state, quieting or calming the patient without affecting clarity of consciousness."

Defining a drug by its effects, however, can be misleading. The same effects by which the dictionary defines a tranquilizer have sometimes been seen after administration of a sedative — or, for that matter, a placebo.

Ambiguous though the term may be, it appears to be here to stay. The 1966 edition of the Physicians' Desk Reference[4] lists 42 tranquilizers indicated for treatment of anxiety and apprehensive states.

'Tranquilizers' have differences in action, differences in effect

Although all tranquilizers are intended to calm anxious patients there *are* differences in their actions — and in their effects. They have been divided into three categories — the rauwolfia group, the 'minor' tranquilizers, and the phenothiazines.[5]

Although the tranquilizing effect of rauwolfia has been known for centuries, its use as an antipsychotic agent in current practice has diminished.[5]

A 'minor' tranquilizer is often prescribed to achieve more than one effect. Thus, besides being tranquilizers some of these compounds may be muscle relaxants, antihistaminics with some calming action, anticholinergic sedatives, or antispasmodics.[5]

The phenothiazines are considered 'major' tranquilizers because they alter psychotic behavior.[1] This classification may have done them more harm than good because it implies that the phenothiazines should be reserved for the more severely disturbed. This is not necessarily true.

The phenothiazines — and the problem of sedation

One of the problems of prescribing phenothiazines for ambulatory patients has been the fear that excessive sedation will impair the patient's ability to function. This, however, is less of a problem with some of the phenothiazines.

"Clinically they may be differentiated primarily in terms of their potency and the extent of their sedative effect, which appear to be inversely proportional. That is, the least potent, the one which is used in highest dosage, chlorpromazine, is the most sedative, while the reverse holds true for fluphenazine."[6]

In a recent report on various studies conducted over several years evaluating 360 patients treated for anxiety and stress with seven phenothiazines, this inverse relationship of potency to sedation was confirmed.[7] Also under consideration was the degree to which the particular phenothiazines neutralized anxiety (the angolytic index). Interestingly enough there was, again, an inverse relationship. The most sedative of the phenothiazines appeared to be the least active in neutralizing anxiety. Fluphenazine, one of the least sedative, on the other hand, was found to be most effective in relieving anxiety.[7]

RELATIVE SEDATIVE AND ANGOLYTIC INDICES OF PRINCIPAL PHENOTHIAZINES*

DRUG	SEDATIVE INDEX	ANGOLYTIC INDEX	BASED ON STANDARD DOSE OF
Chlorpromazine	100	15	25 mgs.
Triflupromazine	100	15	25 mgs.
Thioridazine	90	17	25 mgs.
Perphenazine	15	25	4 mgs.
Carphenazine	25	25	25 mgs.
Trifluoperazine	3.3	95	2.0 mgs.
Fluphenazine	3.5	100	2.5 mgs.

*adapted from Sainz[7]

Prolixin is therapeutically effective without excessive sedation

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Contraindications: Do not use with high doses of hypnotics or in patients with subcortical brain damage. Use with caution in patients with a history of convulsive disorders. Severe reactions may occur in patients with idiosyncrasy to other centrally-acting drugs, and severe hypotension may occur in patients with special medical disorders, e.g. mitral insufficiency and pheochromocytoma.

Precautions: Effects of atropine, anesthetics and C.N.S. depressants may be potentiated. Hypotension may occur in patients undergoing surgery. Do not use epinephrine for treatment of the hypotensive reactions which may appear in patients on phenothiazine therapy.

Side Effects: Extrapyramidal reactions, allergic skin reactions, the possibility of anaphylaxis, drowsiness, visual blurring, dizziness, insomnia, nausea, anorexia, salivation, edema, perspiration, dry mouth, abnormal lactation, polyuria, hypotension, and jaundice and biliary stasis may occur. Routine blood counts are recommended to determine possible blood dyscrasias; if symptoms of upper respiratory infection occur, discontinue drug and institute appropriate therapy.

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For full prescribing information, see package insert.

References: 1. Simpson, G.M.: Postgrad. Med. 39:557, 1966. 2. Freyhan, F.A.: Am. J. Psychiat. *115*:577, 1959. 3. Dorland's Illustrated Medical Dictionary, ed. 24, Philadelphia, W. B. Saunders Co., 1965, p. 1603. 4. Physicians' Desk Reference, 1966, Oradell, N.J., 1965, p. 310. 5. Cohen, S.: Northwest Med.: 65:197, 1966. 6. Detre, T., and Jarecki, H.: Connecticut Med. 25:553, 1961. 7. Sainz, A.: Psychosomatics 5:167, 1964.

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8-12 yr. . . 1 tsp. 5 times daily (10 mg.)

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(or 2 tablets q.i.d.)

*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the initial daily dosage.

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Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness, insomnia, numbness of extremities, headache, blurring of vision, swelling of the gums, euphoria, depression and general malaise.

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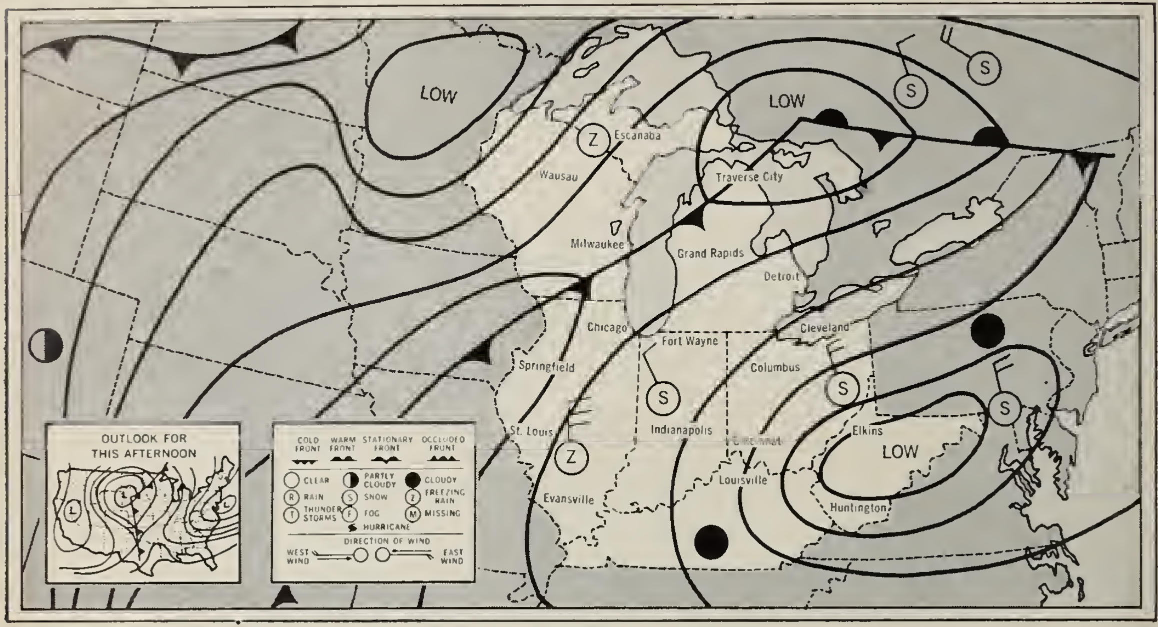

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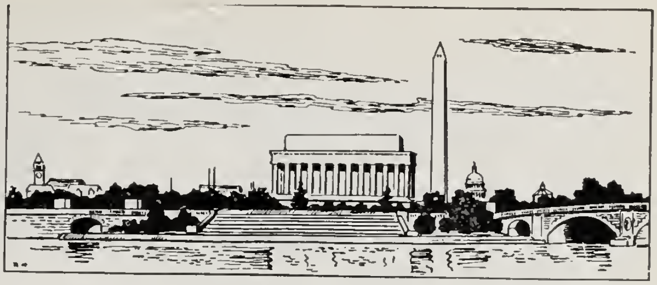

EDITORIALS

"A Time To Be Born . . . And To Be A Child"

Early in November, with December deadlines rapidly approaching, is a difficult time to be thinking of a Christmas editorial. As I was deploring the fact that we had no Christmas message of any kind for December, it happened, as sometimes does, that a windfall appeared. It came within the pages of the *Bulletin of the Greene County* (Missouri) *Medical Society** in the form of a contribution from the Editor, Dr. Wilfred E. Wooldridge. In a humorous and rueful vein he states what I am sure has often occurred to many of us, particularly at this time of year: the loss to children of simple joys. But let Dr. Wooldridge say it.

"Did you ever stop to think that this is a mighty tough age for a child to try to be a child? This thought has occurred to me before, as I noted today's various pressures which did not confront me when I was a tadpole. However, I was never quite as forcefully reminded as when I picked up a catalog from among our mail at home. This catalog was devoted to children's playthings and its central theme was that parents were guilty of neglect of their offspring if they failed to initiate a program of planned play as soon as the umbilical cord was tied. The catalog was cleverly named 'A Head Start For Your Child,' a title aimed to set aglow any incipient PTA member.

"The first page of the catalog was called 'Don't Waste Infancy.' Here was a pitch designed to sell a baby-see mirror, touch perception cylinders, a special teething machine, and even an LP record of highly selected slumber songs. Without question, these lullabys were chosen at great effort by the Infancy Ad Hoc Committee on Sleep.

"From there we went through Touch, Tasting and Feeling to Handling, Fitting and Sorting, thence to Walking, Climbing and Pulling. Obviously the old spoon I teethed on, the stew pan I beat hell out of with the spoon, and the woolly dog which bore me during my first halting steps were disgracefully barbarian. Nobody planned them.

"And that's only the beginning, folks. From that point children must begin learning Spanish when fresh out of diapers, although I have never yet talked to a kid who wouldn't freely agree that he looked back on it as an infernal waste of time. They must study interpersonal relationships when half those in high school can't even spell 'interpersonal relationships.' They must delve into rings and sequences of numbers when the question, 'If 6 people have 9 apples each, how many do they have all together?' will be met only with blank stares.

"This is not to say that educational processes cannot be improved upon, but it seems rather silly to assume that all the wonders of childhood can be satisfied, best and only, by a bunch of adults who can figure it all out and come up with ridiculous merchandise at rather exorbitant prices (that teething ring costs $3.50).

"If we only stop to think, we adults will blush and admit that the most elemental surroundings are enough to bring the budding child into full bloom—so long as the child is bolstered with kindness and consideration and love. The imagination of a happy child is beyond the comprehension of us all, and it needs few stage props. That beautiful paragraph from the Lounsbury will puts this all so well:

" 'I devise to children the banks of the brooks and the golden sands beneath the waters thereof, and the odors of the willows that dip therein, and the white clouds that float high over the giant

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* October, 1966 Bulletin (Volume 25, page 5), published in Springfield, Mo., and reprinted here by permission of the author.

Opinions expressed in contributions to the Editorial Section are those of the writers and do not necessarily reflect the views of the Medical Society of the District of Columbia

trees. And I leave to them the long days to be merry in, in a thousand ways, and the night and the moon, and the train of the Milky Way to wonder at.'

"Yes, we could do nicely with less planned childhood, but a little more planning for parenthood might not be so bad."

If you agree with Dr. Wooldridge, I hope you will spread the message. So, a Merry Christmas, and I hope that you and yours will have something this year to "wonder at" that was not store bought.

A. L. E.

The Significance of an Endowed Chair in Pharmacology*

Pharmacology is one of the traditional 6 basic sciences of medicine along with anatomy, biochemistry, physiology, pathology and microbiology. In our schools of medicine, and in our schools of dentistry, pharmacology is a course usually taught in the first or second year of the 4-year curriculum. But pharmacology is much more than that. It far transcends a course for sophomore medical students and dental students. It is the science of the basic mechanisms of drugs at the cellular level, and at the same time it is the science of the application of drugs in the treatment of human disease. It is a science which concerns itself with the chemical structure of pharmacologic agents and their biochemical interactions, and at the same time it is the science which concerns itself with adverse clinical reaction to drugs, such as abnormalities of the fetus, depression of the formation of blood cells, and skin rashes. And so, the science of pharmacology draws on all of the other basic medical sciences and is an integral part of the clinical sciences—medicine, pediatrics, obstetrics, psychiatry and surgery.

The Department of Pharmacology at Georgetown University was one of the first 5 departments of pharmacology in the United States. It has had a distinguished history, particularly under Dr. Theodore Koppanyi, its Chairman since 1930. Dr. Koppanyi has served as Chairman of the Department of Pharmacology at Georgetown longer than any other Professor of Pharmacology in the United States. This year Dr. Koppanyi will relinquish his chairmanship of the department, giving up his administrative duties to devote his full time to teaching and research.

It is most fitting that the first endowed chair in Georgetown's Medical Center is the chair in pharmacology. The Chairman of the Department of Pharmacology is an important administrator of the University, a vital planner and teacher in our educational programs, a leader of our research effort, and an essential link between the University and those private and Federal agencies that are concerned with the Nation's health.

The wisdom and farsightedness of the Schering Foundation are most evident. With its gift, Schering is setting an example for all potential givers in what we now commonly refer to as the "private sector." Medical education and research have benefited enormously from Federal programs and appropriations. But, essential to the survival and the growth of medical education, particularly in the private universities, are the interest and the material support of private industry. I am sure that many of you are familiar with the efforts of the National Fund for Medical Education in marshalling the forces of private industry in support of medical education in the United States. This effort has occasionally faltered in the past. I cannot emphasize too strongly the importance of private giving for the survival of medical education as we know it today.

The Schering Foundation is to be congratulated on this far-reaching decision. Its gift will benefit future generations of citizens.

John C. Rose, M.D.
Dean, Georgetown University
School of Medicine

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* Remarks prepared for delivery upon announcement on September 15, 1966, of a grant for an endowed Chair in Pharmacology from Schering Foundation, Bloomfield, N. J.

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Community Health Week 1966

SUMMING UP THE RESULTS of the D. C. Medical Society's second annual promotion of Community Health Week, October 16–22, Dr. Robert J. Coffey, President of the Society, described the project as one of the most successful community activities the Society had ever sponsored. He said he was especially appreciative of the fine coöperation given by the many participating doctors, the D. C. Health Department, various voluntary health agencies, and by all news media.

A new dimension was added to Community Health Week this year with an invitation to the public to take free tests in the Society's Exhibit Hall during the first 4 days of the Week's observance. A number of health agencies also set up displays, and attendant personnel were present for the 4 days to answer questions and distribute literature. A total of some 1,700 persons came in for the tests for glaucoma, syphilis, blood typing, hearing tests, and chest X-rays at the Society's building and at the Washington Hospital Center and D. C. General Hospital.

President Coffey said a special vote of thanks was due Dr. Warren D. Brill, Chairman, and Dr John M. Keshishian, Vice Chairman, of the Society's Committee on Public Information and Education, and to all the members of the Committee for their efforts in making Community Health Week the success it was.

KIWANIS INTERNATIONAL
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MARYLAND
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THE CAMERA RECORDED SOME HIGHLIGHTS OF COMMUNITY HEALTH WEEK 1966. These photographs give some indication of the kind of community leadership and participation which made the Week a successful project.

1. The Washington Society for the Prevention of Blindness coöperated in glaucoma testing; Dr. Ronald S. Deitch is doing the examination on this "patient."

2. Bob Raiford (standing) of Radio-WTOP briefs Dr. Charles E. Townsend (left) and Dr. Melchior Savarese prior to their participation in "For Your Information" program. They were on the air for 55 minutes answering questions phoned in by the public about the contraceptive pill and related subjects. WTOP reported that the program was one of the most exciting and interesting ever broadcast.

(*Continued on page 685*)

Frankly, most antihypertensives are pretty good if you give an adequate dose. I'm looking for one with a simple regimen so that mix-ups in doses and therefore the chance of side effects are minimized.

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Precautions: Reduce dosage of concomitant antihypertensive agents by one-half. Discontinue if the BUN rises or liver dysfunction is aggravated. Electrolyte imbalance and potassium depletion may occur; take particular care in cirrhosis or severe ischemic heart disease, and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use with caution in patients with ulcerative colitis, gallstones, or bronchial asthma.
Side effects: Nausea, vomiting, diarrhea, muscle cramps, headaches and dizziness. Potential side effects include angina pectoris, anxiety, depression, drowsiness, hyperglycemia, hyperuricemia, lassitude, leukopenia, nasal stuffiness, nightmare, purpura, urticaria, and weakness.
For full details, see the complete prescribing information.
Availability: Bottles of 100 and 1000 tablets.

Geigy

Consent for Use of Investigational New Drugs on Humans

Statement of Policy (21 CFR 130.37)*

We have given careful consideration to the "new statement of policy" governing consent for use of investigational new drugs on humans which appeared in the August 30, 1966 issue of the *Federal Register*, and submit herewith our comments.

Section 505 (i) of the Federal Food, Drug, and Cosmetic Act provides that regulations on the use of investigational new drugs shall impose the condition that investigators "obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interest of such human beings." There is nothing in that Section which grants the Food and Drug Administration authority to impose its opinion of what constitutes consent upon the medical profession. The "consent" provision was enacted as a measure to assure that medical practitioners protect the human rights of individuals in the investigation of new drugs. These rights do not emanate from the Food, Drug, and Cosmetic Act—to be defined, amplified, or interpreted by the Commissioner. They exist in the entire body of civil law.

It is impossible for the Commissioner to codify realistically, in the form of a policy statement, the legal requirements for valid consent under the myriad varying circumstances which exist. There are thousands of pages of case law which perform that function. The court in each case does and must take into account the particular fact pattern involved. Also considered is the discretion that must be left with the individual practitioner if he is to be able to best serve his patient. The manner in which the proposed regulation has been drafted makes it appear that the FDA, in one policy statement, is attempting a codification of that entire body of law. For example, the comprehensive criteria set forth as necessary for an "informed consent" are seemingly derived from recent court decisions. Yet, among other things it would appear from the statement that a "representative" has unlimited legal authority to give valid consent to the administration of investigational drugs to a child or institutionalized incompetent person, etc., primarily for the accumulation of scientific knowledge.

From the standpoint of proof it may be better, if the need arises, for the physician to have the patient's consent in writing. However, the requirement that such consent shall be in writing exceeds existing legal requirements for a valid consent and constitutes an unwarranted interference with the practice of medicine. The use of investigational drugs does not always involve unusual hazards, and it should be left to the physician's discretion as to whether a written rather than an oral consent should be obtained.

In providing that the "patient's consent shall be obtained in writing by the investigator," is it

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* These comments were submitted by F. J. L. Blasingame, M.D., Executive Vice President of the American Medical Association, in the form of a letter, September 28, 1966, to James L. Goddard, M.D., Commissioner of the Food and Drug Administration, in which the AMA presents a statement of its policy toward FDA regulations regarding consent for use of investigational new drugs on humans.

(*Continued from page 683*)

3. Bill Trumbull, WMAL radio personality, is interviewing Dr. Stacy L. Rollins (right) on the progress of Community Health Week.

4. Dr. Orville W. Donnelly (left) is greeted by John Pettit, President of the Downtown Jaycees of Washington, D. C. just prior to the luncheon at which Dr. Donnelly was the speaker.

5. Dr. Robert J. Coffey (left), President of the D. C. Medical Society, was the guest speaker at the Bethesda Kiwanis Club's weekly luncheon. He is greeted by Walter Schilling, President of the Club.

6. Dr. James A. Kehoe (left) discusses C.H.W. with Dick Morgan, host of the WTTG-TV Community Billboard show.

7. Woman's Auxiliary in the Spotlight: WRC-TV personality Inga interviews Mrs. Thomas N. Carter, President of the Woman's Auxiliary to the D. C. Medical Society. Others in the photo are also members of the Auxiliary. They greeted people during C.H.W. who came into the Society's headquarters for the free medical tests.

8. Barbara Coleman, of "Here's Barbara Program" (WMAL-TV), questions Dr. Peter N. Horvath on medical subjects of general interest to the public.

9. The Lineup: These people are waiting for hearing tests and to have their blood typed. The blood testing was supervised by the Metropolitan Washington Blood Banks and the hearing tests, by the Washington Hearing Society.

Drs. Rollins, Donnelly, Kehoe, and Horvath are members of the Medical Society's Committee on Public Information and Education.

intended that written consent shall be obtained only in the case of a patient but not a subject? Is it intended that written consent shall be obtained from a patient but that oral consent is sufficient when a representative acts on his behalf? Is it necessary that the patient's written consent be obtained only by the investigator, or can it be obtained by someone else? Does the "fair explanation of all material information" have to be stated in the written consent, or will a simple statement of consent to the administration of the investigational drug suffice?

In our opinion, the policy statement exceeds the authority delegated to the Commissioner, contains ambiguities which would result in confusion concerning the legal responsibilities of physicians in the investigational use of new drugs, and is an unwarranted interference with the practice of medicine. We urge, therefore, that it be withdrawn. In any event, we request that its effectiveness be stayed until representatives of the various interested organizations and the FDA have had a full opportunity to discuss the statement and explore alternatives.

Reimbursement under Medicare for Hospital-compensated Physicians

Final regulations governing reimbursement under Medicare for the services of physicians who are compensated by and through hospitals were published in the *Federal Register* on October 13, 1966.

In announcing publication of the regulations, Robert M. Ball, Commissioner of Social Security, noted that under the Medicare legislation a hospital-based physician's services to individual Medicare beneficiaries in the hospital are covered under the supplementary medical insurance part of the Medicare program. Other services provided in a hospital, including teaching, administration, and other physician services that benefit patients as a group rather than individually, are covered under the basic hospital insurance part of Medicare.

Hospitals may continue to follow the usual practice of billing for the services of the hospital-based physician along with the related costs—if this is acceptable to the physician—or the physician may bill the patient directly for his services to the patient. Under either method of billing, however, Mr. Ball said, the charges for services the hospital-based physician furnishes to individual patients must be separately identified for Medicare reimbursement purposes and billed to the medical insurance plan, while hospital costs associated with the services must be billed to the basic hospital insurance plan.

The regulations are carefully designed to leave physicians and hospitals entirely free to determine arrangements between them—to follow their existing local practice, or to make any new arrangement they may decide upon.

Mr. Ball reported that 3 substantive changes have been made in the principles. In addition, a fuller explanation of the practical and legislative rationale has been included, and some areas of apparent misunderstanding have been clarified.

Under one change, the optional simplified billing method, limited to pathologists and radiologists under the principles as previously proposed, may be used in billing for other services. Under the final regulations, this optional method, involving the use of a uniform percentage for determining the amount of hospital-based physicians' charges, may be used in figuring the charges for any physician's services which have not been separately identified under previous billing practices of the hospital.

Another change affects hospitals which do not itemize services rendered to individual patients but rather include them in the institution's general overall charge for services. The change makes it unnecessary for these institutions (mainly tuberculosis and psychiatric hospitals) to itemize physicians' services for Medicare purposes and permits payment under the program on a per diem or per visit basis.

The third modification takes account of the situation where a physician providing patient care in a hospital is paid for these services by a medical school, a state, municipality, or other private or public organization. Under the final regulations the compensation received by the physicians from such sources can be taken into account in determining the physicians' charges that are reimbursable under the medical insurance part of the Medicare program.

Project Vietnam Reaches Successful Conclusion

RICHARD E. PERRY, M.D.*

St. Petersburg, Florida

MANY MAGNIFICENT foreign aid projects, including dams, highways and power plants, have been erected in Vietnam. These projects are vital, but none has really impressed the mass of people upon whose support we depend to resist Communist advances. What does impress the Vietnamese people is aid that affects an individual, such as an American physician converting a crippled child into a healthy child or a wounded farmer into a working farmer. In communicating with the Vietnamese none of our efforts is as effective as the busy tongues of a hundred mothers or wives spreading the word about what great things American medicine can do.

It was my privilege to be the first volunteer to serve in Vietnam under the sponsorship of Project Vietnam. This pilot program sent U.S. physicians to help meet the vital medical needs of Vietnamese civilians who had only 1 doctor for every 23,000 people. While Vietnamese physicians total 700, 500 of these are serving in the armed forces.

Shortly after my arrival other volunteers came to do their part in helping to alleviate the suffering of the Vietnamese people. Soon we were represented in 18 province hospitals throughout the country and, at the completion of our first year, 119 U.S. physicians had served.

Ineffective foreign aid programs which we sometimes hear about are discouraging, but it is not conceivable that such a problem could arise with programs such as Project Vietnam. A physician volunteer has nothing of material value to give directly and assists only by providing a service in treating the ill or wounded, or by imparting his knowledge to his Vietnamese colleagues. The volunteer physician offers a person-to-person type of aid which is recognized as such by the recipients.

It has been said that Orientals do not wish to change their way of life. With this I emphatically disagree, and I can speak from my experiences not only with Project Vietnam but for 2 years previously in Saigon with Project HOPE. Once Orientals are shown a way—a hope or an opportunity to improve their lot—they pursue it aggressively. Project Vietnam has helped the Vietnamese people to fight their way out of an environment of adversity, poverty and disease rather than accepting it as their heritage.

Much of the credit for the success of Project Vietnam goes to Dr. William B. Walsh and The People-to-People Health Foundation, Inc., of which he is founder and President. Responding to a request a year ago by President Johnson, Dr. Walsh organized Project Vietnam with the same skill and effectiveness which has marked the highly successful Project HOPE. The volunteers Dr. Walsh recruited, including myself, served under near-combat conditions in a hot, steamy climate where even the best of facilities were grossly inadequate. As in Project HOPE each volunteer served without pay for a minimum of 2 months.

The success of Project Vietnam at the end of its first year is attested by the fact that the pilot project has now become a permanent program. Under a new contract with the Agency for International Development, which funds the project, the American Medical Association has assumed permanent guidance of the program under the name of "AMA Volunteer Physicians for Vietnam." This program will provide an opportunity for the medical profession in our country to demonstrate once again their tradition of service to fellow men.

Upon completion of the pilot project, Dr. Walsh received the following letter from David E. Bell, Administrator of the Agency for International Development:

"One year ago President Johnson appealed to the physicians of this country to help meet the

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* EDITOR'S NOTE: Dr. Perry, an orthopedic surgeon, served as Director of Project HOPE's Orthopedic Rehabilitation Center in Saigon, Vietnam, from July 1962 to March 1964. Upon his selection in August 1965 as the first volunteer for Project Vietnam, Dr. Perry received a personal commendation from President Johnson at the White House.

The pilot project, Project Vietnam has now come under the permanent guidance of the American Medical Association and is designated, AMA Volunteer Physicians for Vietnam. An early issue of the MEDICAL ANNALS will describe the plans being developed under its new sponsorship.

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urgent needs of the civilians in war-torn Vietnam. This Agency was charged with the administration of the program for volunteer physicians. There was no certainty at that time that American doctors would respond in significant numbers to serve without pay under near-combat conditions. You were among the first to assure us that the challenge would be met by the medical profession in the finest tradition of humanitarian service.

"In response to a request by this Agency, you as President of The People-to-People Health Foundation, Inc., assumed the direction of a pilot program to test the conceptual validity of such a volunteer program. Now a year later the facts speak for themselves. Between July 1965 and June 1966 119 physicians representing 10 different disciplines have served at 18 Vietnamese civilian hospitals throughout the country. In gratitude the Government of Vietnam has decorated a number of these fine men. And each of them has received this Agency's Special Certificate for service.

"As the pilot phase of this program draws to an end, however, it is only fitting that official recognition be given to the indispensable role which you have played in organizing and implementing this most patriotic endeavor. On behalf of the Agency for International Development, I wish to express my personal appreciation and esteem."

I believe the sentiments of Mr. Bell are shared by all of us who had the opportunity to serve in Vietnam.

Health Dept. Notes

Low Cost Drug Program for Rheumatic Fever and Rheumatic Heart Disease Patients

A Low Cost Drug Program to enable rheumatic fever and rheumatic heart disease patients under private medical care to have drug prophylaxis at lower costs was inaugurated last month. This is part of the Rheumatic Fever Program which was started by the D. C. Department of Public Health during 1964.

The basic purposes of the Rheumatic Fever Program are 2-fold: First, it provides a systematic follow-up of all rheumatic fever and rheumatic heart disease patients in the District through the use of a patient register. Hospital and clinic records for the past 7 years were reviewed to locate all persons in D. C. with a history of these diseases. Each record in the register contains identifying information together with rheumatic fever history and recurrences, current medical status, treatment, and date of latest medical supervision and treatment.

Second, the need for medical supervision of the patient is emphasized. The patient is encouraged to return to his physician for continuing care. Clinics are asked to prepare for the Department a yearly follow-up report, including the current medical status of the patient and drug prophylaxis.

Upon request of a physician or clinic, follow-up procedures are started for patients who have lapsed from medical supervision. These patients may be contacted by letter, telephone, or a visit from a Health Department representative.

The Department is unable to force a rheumatic fever or rheumatic heart disease patient to participate in this program. The private practitioner is faced with an equally difficult problem of recalling a delinquent patient to the physician's office. It is anticipated that the provision of drugs at low cost will encourage patients to return for physicians' care.

Minimal recommendations in the current Rheumatic Fever Program are: Individuals with diagnosed cases of rheumatic fever without heart involvement should continue daily antibiotic prophylaxis until age 21; those individuals with cardiac involvement should continue daily prophylaxis until age 40. Private physicians will decide which of their patients should participate in the Low Cost Drug Program.

The following procedure has been devised: The physician desiring this service will send patient information to the D. C. Medical Society and in turn will receive a booklet containing 4 prescription blanks for each patient. The 4 blanks cover a year's supply of penicillin which the physician, at his discretion, may prescribe for the patient. The prescription may be filled at a participating pharmacy of the patient's choice. The price of 100 tablets of penicillin G, 250,000 units, does not exceed $2.25.

Coöperating with the Department in this program are the Medical Society of the District of Columbia, the Medico-Chirurgical Society of the District of Columbia, the District of Columbia Pharmaceutical Association, and the Washington Heart Association.

Since the program began in 1964 the records of approximately 3,000 persons with a diagnosis of rheumatic fever or rheumatic heart disease have been reviewed. There are approximately 1,000 persons on the rheumatic fever register. Those persons whose records did not indicate rheumatic fever or heart disease or could not be located were not placed on the register.

Since the register was established, 254 persons who had lapsed from medical treatment were encouraged to return for medical supervision.

A breakdown of the 413 people on prophylaxis by age group shows:

Age	Number
Under 14 years of age	100
15–19 years of age	113
20–24 years of age	65
25–44 years of age	113
45 years and over	22

It is our intention to prevent rheumatic heart disease through the active coöperation of the private practitioner, the Health Department, the local pharmacist, and the local voluntary health agencies. The Low Cost Drug Program will help to achieve this goal.

Murray Grant, M.D., D.P.H.
D. C. Director of Public Health

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D. C. Medical Assistants' Annual Symposium

The D. C. Association of Medical Assistants, with President-elect Gail Thornburg presiding, held its Annual Scientific Symposium and Luncheon on October 29 in the South American Room of the Hotel Statler-Hilton. The theme of the meeting was "General Advances in Medicine." Effective presentations were made on the following subjects by 5 guest speakers:

"Techniques in Plastic and Reconstructive Surgery." Dr. Gordon S. Letterman, Professor of Plastic Surgery, George Washington University School of Medicine

"The Kidney Machine: Its Development, Use, and Economics." Dr. Alvin E. Parrish, Professor of Medicine and Director of Clinical Research, George Washington University Hospital and School of Medicine

"Orthopedics," including common bone deformities, posture correction, etc. Dr. Robert C. Rush, Clinical Assistant Professor of Orthopedics, Georgetown University School of Medicine

"Child Psychiatry: Office Techniques." Dr. Larry B. Silver, Career Fellow in Child Psychiatry, Children's Hospital

"Diabetes." Dr. William Kurstin, member of the attending and teaching staffs of the George Washington University Hospital and Doctors Hospital

Following each presentation the speaker answered questions from the audience.

Mrs. Imogene Warner (Dr. Samuel Dodek) reported on the Tenth Annual Meeting of the National Association, which was held in St. Louis, October 18–23. Six members were present from Washington. National plans include a survey of courses presently offered by accredited community colleges with the objective of establishing training standards and recognizing schools which meet those standards. Merck Sharp & Dohme is supporting such a school approval program with a $5,000 grant; at the St. Louis meeting the announcement was made that Lederle Laboratories is augmenting this fund with a $5,000 grant.

Mrs. Warner, immediate Past President of the D. C. group, is serving as National Historian for 1966–67.

The District of Columbia Association of Medical Assistants is an affiliate of the American Association of Medical Assistants, with headquarters in Chicago. The local group now has more than 80 members. The following members served as officers for 1966 (in parentheses are their physician-employers):

President: Mrs. Pearl Knowles (Drs. Horstman and Swift)
President-elect: Miss Gail Thornburg (Drs. Kleh and Gruver)
Vice President: Miss Dorma Schnurr (Drs. Peabody and Lyons)
Secretary: Miss Mary Libert (Drs. Horstman and Swift)
Assistant Secretary: Miss Suzanne Earley (Dr. Harold Silver)
Treasurer: Mrs. Allegra Kelly (Dr. Elmer Rones)
Assistant Treasurer: Miss Alma Carter (Dr. E. C. Mazique)

Meetings are held each month on the first Wednesday or Thursday, alternately, at 8 p.m. in the D. C. Medical Society Building. An address by a guest speaker in medicine highlights each program and is followed by a short business session, discussion period, and a social hour with refreshments.

Alice D. Furlong (Dr. Frank Sanzaro)
Publicity Chairman, D. C. Association of Medical Assistants

Patients Needed for Clinical Center Studies

The coöperation of physicians is requested in the referral of patients for the following studies being conducted at the Clinical Center of the National Institutes of Health in Bethesda, Md.

A study of **lymphosarcoma and reticulum-cell sarcoma** in children and young adults is being conducted by the Medicine Branch of the National Cancer Institute. All clinical states of biopsy-proven disease are acceptable, and untreated patients are preferred. Slides of pathologic material must be submitted for review before patients can be accepted.

Of particular interest are those patients with clinical and histologic features similar to the malignant lymphoma of African children (Burkitt tumor). These patients generally present with jaw, ovarian, or abdominal masses. The purpose of this study is to conduct immunologic, virologic, pathologic, and chemotherapeutic studies.

Suitable patients will be admitted to the Clinical Center in Bethesda, Maryland, or to one of the participating medical centers. Physicians who wish to have their patients considered for the study may write or telephone Dr. John L. Ziegler, Clinical Center, National Institutes of Health, Building 10, Room 12-N-226, Bethesda, Md. 20014; telephone: 656-4000, Ext. 64251.

Patients with the highly suspicious or proven diagnosis of a **carotid body tumor** are needed for a study being conducted by the National Cancer Institute and the National Institute of Arthritis and Metabolic Diseases. The purpose of this investigation is to relate histochemical evidence of catecholamine containing cells in carotid body tissue to excretion of catecholamines and their metabolites.

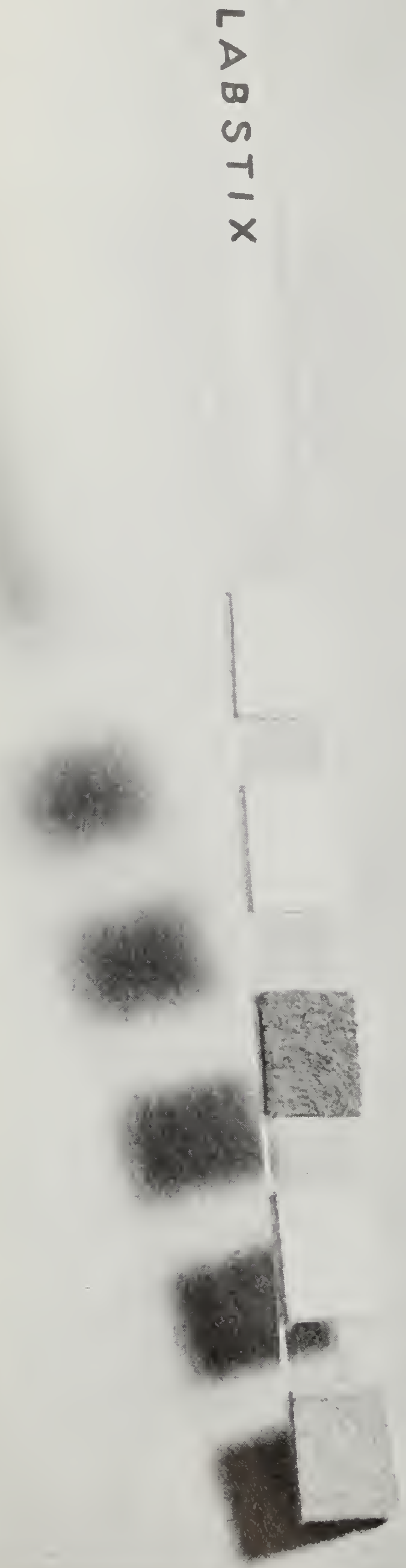
Patients admitted will be evaluated for definitive treatment. Upon completion of their study, the referring physician will be contacted concerning the indications for treatment and a coöperative decision made as to whether the treatment be best carried out at the Clinical Center or back in the hands of the referring physician.

Physicians interested in having their patients considered for admission to this study may write or telephone Dr. Alfred S. Ketcham, Clinical Center, Room 10-N-116, National Institutes of Health, Bethesda, Md. 20014; telephone: 656-4000, Ext. 64164.

Patients with **diseases of the endocrine glands** are needed for a study being conducted by the Endocrinology Branch of the National Cancer Institute. Methods have been developed for measuring plasma androgens and gonadotropins and estrogens. These hormones are being studied in patients with breast cancer, hypogonadism, pituitary tumors, and virilization.

Patients with early metastatic breast cancer are needed for study and treatment. Patients with diseases of the gonads or pituitary will be accepted for diagnosis and initiation of therapy.

Physicians interested in having their patients considered for admission to this study may write or telephone Dr. Mortimer B. Lipsett or Dr. Griff T. Ross, Clinical Center, Room 12-N-204, National Institutes of Health, Bethesda, Md. 20014; telephone: 656-4000, Ext. 62021.



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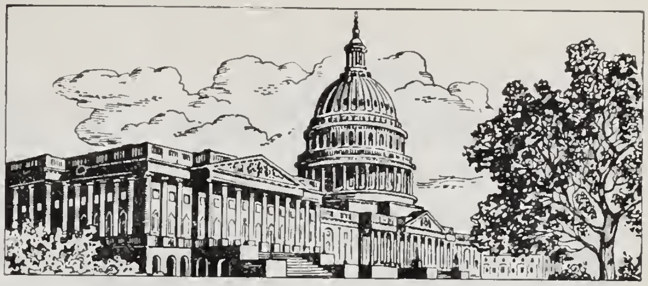

NEWS & PERSONALS

Summary of Executive Board Actions

Proceedings of October 3 Meeting

On October 3, 1966, the Chairman of the Executive Board, Dr. J. Spencer Dryden, called the meeting to order at 7:00 p.m. in the headquarters' Board Room. Present were Drs. C. Willard Camalier, Jr., Robert J. Coffey, Henry D. Ecker, Claudine M. Gay, Raymond T. Holden, Edward W. Nicklas, Paul R. Wilner, and Mr. George W. Cooley, Secretary. Also present were Dr. Oscar B. Hunter, Jr., and Dr. William C. Swatek, representing the Section on Pathology and Laboratory Medicine.

The minutes of the meeting of August 29 were approved.

Committee Meetings: The Secretary reported that the following committees had met:

August	30	Committee on Alcoholism
September	7	Board of Credentials
	9	Committee on Emergency Medical Service
	21	Board of Credentials
	22	Low Cost Drug Program Conference
	27	Committee on Alcoholism
	28	Committee on Public Information and Education
	29	Medical Bureau Committee

Board of Credentials: On recommendation of the Board of Credentials, the following applicants for membership and changes in membership status were approved:

Active Members

T. Wilkins Davis, 1114 W Street, N.W.
Edward G. Fisher, 2515 Rhode Island Avenue, N.E.
Thomas H. Gresinger, 1712 Eye Street, N.W.
David R. Lawrenz, 2001 Eye Street, N.W.
John Chauncy Skilling, 4909 V Street, N.W.
Ian James Spence, 2001 Eye Street, N.W.
William G. Tompkins, George Washington University Hospital
Karl F. Wieneke, Jr., Georgetown University Hospital

Associate Members

Anillo Narciso, Providence Hospital
Ranville Stopford Clark, 3000 Connecticut Avenue, N.W.
Robert C. Pfeiler, 1700 18th Street, N.W.
Touraj Shafai, 1805 North Quinn Street, Arlington, Va.
Tae Byung Whang, Georgetown University Hospital

Reinstatement

Active: Hyman J. Zimmerman

Transfers

Associate to Active: William H. Clements
Resident-Intern to Associate:: Charles D. Daily, Jr.

A letter from Dr. William H. Stewart, Surgeon General of the U.S. Public Health Service, was read, accepting the Board's invitation to become an Honorary member.

Lay-owned Laboratories: Various questions concerning lay-owned laboratories and the relationship of physicians to such facilities were discussed at length. A series of questions was prepared and the Secretary was requested to forward it to the AMA Judicial Council.

Drug Repackaging Companies: Statements regarding repackaging firms and the dispensing of drugs and appliances by physicians were approved for publication in the Newsletter and/or MEDICAL ANNALS.

P.L. 89–239: The President made a progress report on the Society's Planning Grant application under P.L. 89–239 (Heart, Cancer and Stroke).

Nominating Committee: It was voted that the names of the Nominating Committee not be divulged prior to its meeting.

Annual Business Meeting: Sunday, November 20, 1966, from 4 to 6 p.m., was set for the Annual Business Meeting.

Nominations to Medical Service and GHI: The President presented the following nominees to serve on the Board of Trustees of Medical Service of the District of Columbia: Jack Kleh and Philip H. Philbin, each to a second 3-year term. To serve

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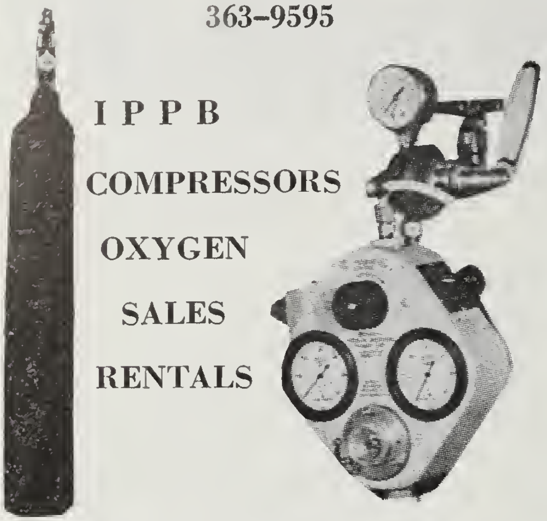

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on the Board of Trustees of Group Hospitalization, Inc. he proposed Paul R. Wilner, to succeed Paul Kiernan, for a 5-year term. These nominations were approved by the Board.

Nominations to Health Foundation of the District of Columbia: The following nominees submitted by President Coffey (the first 3 required by the by-laws) were approved: Robert J. Coffey (President), Henry D. Ecker (President-elect), George W. Cooley (Secretary-Treasurer), Roland B. Scott, Marvin Korengold, and Edward W. Nicklas; also Wilfred Dudley, D.D.S., John McHugh, pharmacist, Grace Matthews, R.N., Renah Camalier, Esq., and Mrs. Jane Yates.

Medical Bureau Committee: The Secretary reported that at a meeting of the Medical Bureau Committee a raise in rates had been recommended of $2 per month for each category of service, although he had requested a raise in rates of $4 for ALS and $6 for TSS. The Secretary presented a comparison of salaries for BUREAU operators with the Telephone Company operators. It was agreed that he should keep abreast of salary scales for telephone operators and maintain BUREAU salaries at similar levels.

Committee on Constitution and By-laws: A report of the Committee on Constitution and By-laws was approved for submission to the membership.

Two resolutions for presentation before the AMA House of Delegates in November were approved.

Meetings

The American Association for the Advancement of Science will meet in Washington, D. C., with headquarters at the Sheraton-Park Hotel, on December 26–31. More than 1,500 scientific reports will be given, relating to the general theme, "How Man Has Changed His Planet." An attendance of 10,000 or more physicians and other scientists, engineers, science educators, and science students is anticipated. The interested public also is invited to attend. The registration fee is $5.00.

A few highlights of the program follow:

December 26: The Moving Frontiers of Science lectures: "The Historical Roots of Our Ecologic Crisis," by Lynn T. White, Jr. (University of California) and "The Changing Man," by Theodosius Dobzhansky (Rockefeller University).

December 27: Invitational address: "The Ever-Widening Gap," by P. M. S. Blackett, Nobel Laureate in Physics, 1948, and currently President, Royal Society, London.

December 28: AAAS Presidential Address: "Untangling Biological Reactions," by Henry Eyring (University of Utah); Moving Frontiers of Science special lectures, "Weather Modification" by Thomas F. Malone (Vice President, Travelers Insurance Companies) and "Problems of Securing Constructive Legislation" by Daniel S. Greenberg (Staff Writer, *Science* Magazine).

December 29: Joint Sigma Xi and Phi Beta Kappa address: "Science, a Wellspring of Our Discontent," by Walter Orr Roberts, Director, National Center of Atmospheric Research.

December 30: Symposia: "The Utility of the Construct of Race" which will include "Behavior-Genetic Analyses and Their Relevance to the Construct of Race," "Biological Aspects of Race in Man," and "Social-Psychological Aspects of Race"; "Migration to the Arid Lands of the United States"; "Biology of the Mouth"; "Therapeutic Incompatibilities Involved in Drug Dosage"; "Role of the Sciences in Management Science"; the annual illustrated lecture and film of the National Geographic Society.

In addition to the scientific reports, 2 other features of the meeting are the Annual Exposition of Science and Industry and the Science Theatre, which will show a choice selection of foreign and domestic science films.

In charge of public information for the meeting is Mrs. Thelma C. Heatwole, 5110 West Franklin Street, Richmond, Va. 23226.

The Georgetown University Medical Center, in coöperation with the D. C. Division of the American Cancer Society, will present a 1-day **seminar on "Clinical Applications of Advances in Cancer Research."** This seminar, which is open to all physicians, will be held on Saturday, March 11, 1967 at the Medical Center. The faculty will be composed of distinguished authorities in cancer management. Preregistration and a fee of $5.00, which includes luncheon and an afternoon reception, will be required. Attendance will be limited and will be determined by priority of registration.

For further information contact the Division of Oncologic Surgery, Department of Surgery, Georgetown University School of Medicine, Washington, D. C. 20007.

General News

The Veterans Administration is offering physicians who qualify a year of training to become **psychiatric clinical investigators.** The training will be in a VA hospital of the trainee's choice, affiliated with one or more of the Nation's leading schools of medicine. A research associate participating in this program will receive an annual salary of $12,873, while having the opportunity to conduct an independent research project.

Candidates are nominated by the VA Research and Education Committee and the Deans Committee of the school of medicine with which the VA hospital is affiliated. Applicants should contact the Director of the VA hospital to which they wish to apply.

Further inquiries about the program may be made to the Director, Research Service, Department of Medicine and Surgery, Veterans Administration Central Office, Washington, D. C. 20420.

An awards program to stimulate teaching, training, and research **in clinical pharmacology** has been established by the **Pharmaceutical Manufacturers Association Foundation.** The PMA Foundation Awards will be offered annually to medical schools for salary support of full-time junior faculty positions in clinical pharmacology.

Applicants for the awards should have at least 1 year of experience in a research training program related to the area of clinical pharmacology and should indicate "a strong determination for a full-time career in clinical pharmacology." The awards are for 2 years each but may be extended for an additional 2 years.

Further details are available from the PMA Foundation, which is located at 1155 15th Street, N.W., Washington, D. C. 20005.

The Pulmonary Disease Division of Howard University College of Medicine and Freedmen's Hospital has been awarded a grant of $35,810 by the National Institute of Allergy and Infectious Diseases to continue studies an additional 3 years on the pathophysiology and etiology of sarcoidosis. The project will be directed by Dr. Roscoe C. Young, Jr., Instructor in Medicine, Howard University, and Director of the Pulmonary Function Laboratory, Freedmen's Hospital. Dr. Thomas G. Shelton, who is also participating in the project, recently presented new findings to the Fourth International Conference on Sarcoidosis, held in Paris, September 12–15.

Dr. Donald Harting, Director of the National Institute of Child Health and Human Development, has accepted a new position in the office of the Director of the National Institutes of Health as Special Assistant to Dr. James A. Shannon. Dr. Harting will have responsibility for the planning and conduct of special studies in association with the NIH Office of Program Planning and the several Institutes and Divisions. He has served in his present position since July 1965.

Dr. Gerald D. LaVeck succeeds Dr. Harting as Director of the National Institute of Child Health and Human Development. He has been Acting Scientific Director of this Institute since last August and was the Institute's Mental Retardation Program Director for the past 3 years. He is Clinical Associate Professor of Pediatrics at Georgetown University School of Medicine.

The Public Health Service of the U. S. Department of Health, Education, and Welfare has **announced 3 new publications.** The first, **"Obesity and Health,"** is a compendium of current information designed to assist the health professions with the obesity problems they encounter in their respective fields of activity.

"Hemophilia" (PHSP No. 1420), issued by the National Heart Institute, contains facts about hemophilia, its causes and treatment.

"Asthma" (PHSP No. 155) is a newly revised publication prepared by the National Institute of Allergy and Infectious Diseases. A 12-page illustrated pamphlet, it points out the danger of allowing asthma to go untreated.

Single copies of all 3 publications are available free from the Public Health Service, Department of Health, Education, and Welfare, Washington, D. C. 20201. The publications are available in quantity at nominal prices from the Superintendent of Documents, Government Printing Office, Washington, D. C. 20402.

Dr. Lionel M. Bernstein, Chief of Medical Service at the West Side, Chicago, Veterans Administration Hospital, has been appointed head of the VA research program; his headquarters will be in Washington, D. C. Dr. Bernstein received his medical degree from the University of Illinois.

Dr. George H. Yeager, founder and **Editor of the Maryland State Medical Journal** since it was first issued in January 1952, relinquished his duties, October 1. He has been **succeeded by Dr. C. Thomas Flotte**, co-Chief of the Department of Surgery and Director of Education at the University of Maryland. He is the author of numerous articles on a wide variety of subjects, notably vascular disease, a special field of interest.

A coöperative relationship between Northern Virginia Community College and the Fairfax Hospital has been established whereby the Hospital will be utilized as a clinical learning setting for students in the College's Associate Degree Nursing Program. The 2-year program, which opened, September 26, with an initial enrollment of 49 students, was developed with the aid of the Virginia State Board of Nurse Examiners and the National League for Nursing. Graduates of the school will be qualified to take the State Board examination for Registered Nurses.

The Multiple Sclerosis Association of Greater Washington has relocated its offices and is now in the Gorman Building at the Georgetown University Medical Center, directly behind the main hospital. The new telephone number is 625–7765.

Personals

Vice Admiral George W. Calver, MC, USN, the first Attending Physician at the Capitol, has retired after serving Congress for 38 years. He was released to inactive duty in brief ceremonies in the office of the Surgeon General of the Navy, October 12. Dr. Calver received his medical degree from George Washington University in 1912 and began his Navy career the following year. In the ensuing 15 years before his appointment to the Capitol in 1928 he became a heart specialist and gerontologist.

BEST WISHES for many golden years are extended to Admiral Calver (right), retiring Physician to Congress, by his successor, Captain Pearson.

Succeeding Dr. Calver is Captain Rufus J. Pearson, Jr., also of the Navy Medical Corps. Formerly Director of Professional Services at the Bethesda Naval Hospital, Captain Pearson was assigned to the Capitol last July, upon Dr. Calver's recommendation. He has been serving as Consulting Editor of the Medical Annals for the past year.

Dr. John Parks, Dean of George Washington University School of Medicine, was voted President-elect of the Association of American Medical Colleges at the 77th Annual Meeting of the Association in San Francisco, October 21–25. He will take office at the 1967 meeting scheduled for Detroit.

The AAMC and the American Medical Association Council on Medical Education established and maintain an accreditation for U.S. and Canadian medical schools. Dr. Parks is a member

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1. Riese, J. A.: Amer. J. Gastroent. 28:541 (Nov.) 1957

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of the AAMC Executive Council and Chairman of the Federal Health Programs Committee. He is also President of the National Board of Medical Examiners and of the Interstate Postgraduate Medical Association.

Dr. Sidney Berman was chosen President-elect of the American Academy of Child Psychiatry at its annual meeting in Dallas, Texas, October 14–16.

Dr. J. Spencer Dryden was reëlected First Vice President of the American Association of Ophthalmology at its meeting in Chicago, October 15–16.

Dr. Allan B. Coleman, Chairman of the Subcommittee on Accidental Poisoning of the American Academy of Pediatrics, was one of 2 pediatricians interviewed in a program series, "Keeping Your Home Safe," to be used for a playing record which will be sent to 1,000 radio stations. The Council on Family Health, of New York, prepared the series. The radio stations may schedule the program as a public service or arrange local or regional sponsorship.

The record will also be sent to the members of Congress to acquaint them with the Council's work, to appropriate Government agencies, to health organizations, and to members of the drug industry.

A team of surgeons from Georgetown University Medical Center, namely, **Dr. Charles A. Hufnagel,** Professor of Surgery, **and Drs. John F. Gillespie and Peter W. Conrad,** Assistant Professors of Surgery, has developed another major aortic heart valve, the fourth produced at Georgetown since 1950. Known as a "unit tri-leaflet valve," it was displayed at the meeting of the American Heart Association at the Hotel Americana in New York, October 21–25.

Dr. John J. Curry, of Silver Spring, Md., an Associate member of the D. C. Medical Society, has been elected Vice President of the Heart Association of Maryland. **Dr. Louis Gillespie, Jr.,** an Active member, was elected to a 3-year term on the Heart Association's Board of Trustees.

Dr. Brian Blades, Chairman of the Department of Surgery, George Washington University School of Medicine, was featured on the cover of the October 10 issue of *Modern Medicine.* He was praised in the cover story for his dedication in training young surgeons and for his work on pulmonary lobectomy.

Dr. J. Robert Andrews, Professor of Radiology and Director of Radiotherapy, Georgetown University Medical Center, attended and participated in several meetings in Japan during October and November. In Tokyo he attended the Ninth International Cancer Congress and served as co-chairman, together with Professor Yamashita of Keio University, of the Section Meeting on Clinical Radiotherapy. He also presented a paper at this meeting and before the Japanese Radiological Society at Matsumoto City, the National Institute of Radiological Sciences in Chiba, and the International Conference on Radiation Biology and Cancer in Kyoto.

Approximately 1,350 surgeons were inducted into fellowship in the American College of Surgeons, October 13, during the Clinical Congress in San Francisco. They included, from the District of Columbia, **Drs. Ernst H. Bremer, James M. Clements, William H. Dickson, John S. Dillon, I. Sidney Jaffee, Stanley M. Kirson, Thomas C. Lee, John W. McTigue, and Leo B. Van Herpe,** all Active members of the D. C. Medical Society except Drs. Clements and Dickson, who are Associate members.

Dr. Jacob Ceppos writes from St. Petersburg, Fla. that he has accepted a position in the Outpatient Department at the Regional Office of the Veterans Administration. Dr. Ceppos practiced in the District for about 27 years before moving to Florida. His address is: 1885 Shore Drive South, St. Petersburg, Fla. 33707. He would be glad to see any members who come down to the area.

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Obituaries

William Glenn Young, M.D., F.A.C.S.

(1878–1966)

Dr. William G. Young, Washington surgeon and urologist for 60 years, died, October 16, 1966 at his home, 3825 Garrison Street, N. W.

Dr. Young was born in Trion, Georgia, December 1, 1878, to William and Sarah Simmons Young. He attended the public schools of Georgia and Tennessee before coming to Washington to attend Columbian College, now George Washington University. He was President of his class when he received his medical degree in 1904. After interning for a year at George Washington University Hospital he did postgraduate work in the Urological Clinic at the New York Postgraduate Medical School and Hospital.

Dr. Young served as Clinical Instructor in Urology at George Washington University School of Medicine from 1922 until 1945. He was on the staff of Providence Hospital from 1908 to 1922 and was appointed to the staffs of Casualty and Emergency Hospitals in 1917. From 1937 to 1945 he was Chief of Urology at Casualty, then President of the Medical Staff 1958 to 1961, and President Emeritus from 1961 until 1964.

In 1907 he was elected a member of both the Medical Society of the District of Columbia and the Medical Association of the District of Columbia, which later merged with the Medical Society. He became a Life member of the Society in 1948. He was a Fellow of the American College of Surgeons and a member of the American Medical Association, the American Urological Association, and the Washington Medical and Surgical Society. He was also a member and Past President of the Hippocrates-Galen Society, the Washington-Baltimore Urologic Society, and the Washington Urologic Society.

He leaves his wife, Mrs. Molly Weaver Young, and 2 sons, Dr. William G. Young, Jr., of Durham, N. C. and Dr. J. Sanford Young, of Oxon Hill, Md. He also leaves 2 daughters, Mrs. Geoffrey Will, of Phoenix, Ariz., and Mrs. Robert S. Schaeffer, of Potomac, Md. A brother, Marvin S. Young, of Tampa, Fla., also survives.

Roy Delaplaine Adams, M.D.

(1881–1966)

Dr. Roy D. Adams, a Life member of the Medical Society of the District of Columbia since 1947, died, October 11, 1966, at Virginia Beach, Va., where he had lived since he retired in 1964.

Dr. Adams was born in Circleville, Ohio, October 26, 1881. He graduated from Georgetown University School of Medicine in 1904 and was licensed to practice in the District of Columbia the same year.

During World War I Dr. Adams served in the Army Medical Corps. He was a founder of the U. S. Veterans Diagnostic Clinic, for which he later served as chief consultant. He was also an instructor in embryology at Georgetown University for several years.

In 1906 Dr. Adams was elected to membership in both the Medical Society of the District of Columbia and the Medical Association of the District of Columbia, which later merged with the former. He was a member of the American Medical Association and the American Clinical and Climatological Association. He belonged to the Chevy Chase Club.

He leaves his wife, Mrs. Helen Baker Adams, and a daughter, Mrs. Helen A. Berndt, of Virginia Beach.

Henry Hardy Lichtenberg, A.B., M.D.

(1903–1966)

Dr. Henry H. Lichtenberg, Chief of Pediatrics and Medical Director Emeritus of Group Health Association of Washington, D. C., died, October 18, 1966, at his home, 5604 MacArthur Blvd., N. W.

Dr. Lichtenberg, a native of New York City, was born to Elias and Jennie Lichtenberg, July 6, 1903. He came to Washington 25 years ago to become associated with Group Health Association and was appointed Chief of Pediatrics. He served as GHA's Medical Director from 1945 to 1961. He was one of the founders of the Association and served on its first Board of Directors.

Dr. Lichtenberg received his Bachelor of Arts degree from Columbia University in 1923 and his medical degree from Columbia University College of Physicians and Surgeons in 1927. During the following years he interned at Mt. Sinai Hospital, New York, Sinai Hospital, Baltimore, and was intern and assistant resident at Johns Hopkins

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Hospital in Baltimore. He was assistant resident in charge of pathology at Children's Memorial Hospital, Chicago, 1930–1931, and Chief Resident in Pediatrics at the same hospital, 1930–1932. The next year he spent at the University of Marburg, Germany as Assistant in Pediatrics at its Children's Hospital. He practiced pediatrics in New York City from 1933 to 1941.

Dr. Lichtenberg was certified by the American Board of Pediatrics. He was elected to Active membership in the Medical Society of the District of Columbia in 1943. He was a member of the American Medical Association, the New York Academy of Medicine, and was a Life member of the Metropolitan Medical Society of New York.

He is survived by his wife, Mrs. Frances Lichtenberg, and a daughter, Louise. A son, James Lichtenberg, resides in New York City. He also leaves 2 sisters, Mrs. Ada Hyers and Mrs. Annie Marmor, and a brother, Meyer Lichtenberg, D.D.S., all of New York City.

Lung Function Tests, Dyspnea, and Work Status—Silver

(*Continued from page 651*)

tions the patient should be informed of our ability to improve the situation so that when the episode is over he will be prepared to return to work. When necessary we may refer the patient for job-training, counseling, or vocational rehabilitation services available in our community. In these ways we relieve unjustified anxiety, combat despair, and prevent the unnecessary "decision to be disabled" which appears to be the easiest solution yet so often proves to be a debilitating one. In these ways our understanding of, and influence on disability become more than the automatic filling out of forms. By helping our patient enjoy both the satisfactions of retaining his personal independence and of doing a useful job we may truly fulfill the physician's traditional and honored role as healer.

Suzanne Early gave valuable assistance in tabulation and data processing for this investigation.

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Anesthesia in Gynecology—Alpert and Barter

(*Continued from page 671*)

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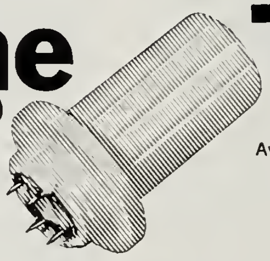

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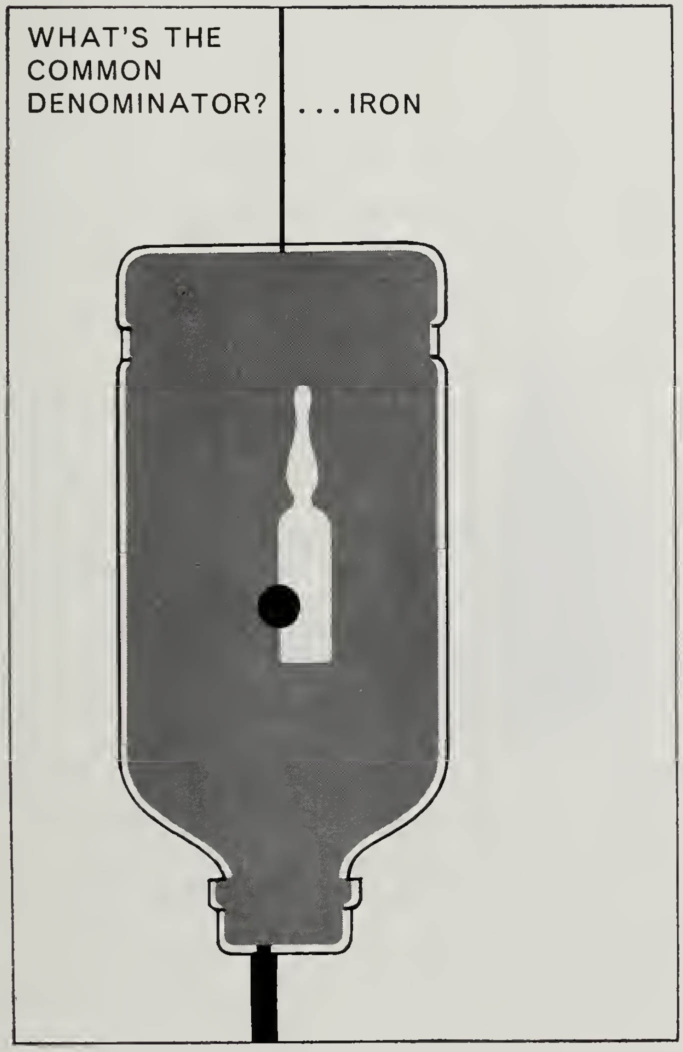

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BOOK REVIEWS

Synopsis of Neurology, 2nd ed. FRANCIS M. FORSTER, B.S., M.D. Price, $7.50. Pp. 218. St. Louis: Mosby, 1966.

The "Synopsis of Neurology" attempts to provide a short summary primarily for use of medical students but apparently for paramedical personnel as well. It consists of 2 sections, one dealing with the neurological examination and the second, greater part with clinical neurological entities. It is therefore a miniature textbook of neurology. There is a real need for a short book to help teach the medical student how to do an adequate neurological examination. Indeed, it does provide practical hints as to how to do a simpler neurological examination, and its treatment of ancillary diagnostic procedures is quite good. One may find confusing, however, the description of the bedside field examination, particularly in the demonstration of a central scotoma.

My criticism lies mainly in its failure to provide a more functional approach to the neurological examination. The difficulty one faces in teaching medical students is compounded by the very format of this book, which copies that of the major neurology textbooks. The larger second section may be unnecessary. This information can be more usefully found in some of the standard 1-volume texts. It may be particularly useless in that it is organized along more traditional lines rather than in anatomical terms. The latter would permit the analysis of the neurological examination to proceed directly into the patterns of weakness, sensory loss, etc. that are directly relevant to localization and the appropriate ancillary diagnostic procedures. Symptomatic of the traditional approach is the description of double simultaneous method of sensory testing as limited to parietal lobe lesions. It is also questionable whether a short book of this sort should concern itself with treatment. Although it is quite up to date, including Sansert®, for example, this again may be superfluous.

It is in general a sound book. I wish, however, that medical students could be provided with not only a short book but one which provides an organized, more dynamic approach.

MARK N. OZER, M.D.

Diseases of the Heart, 3rd ed. CHARLES K. FRIEDBERG, M.D. Price, $22.00 single volume, $26.00 two-volume set. Pp. 1787, illustrated. Philadelphia: Saunders, 1966.

This book of 1,787 pages is the top one in its field today. It is remarkable that one man could have covered such a broad and complicated subject alone and at the same time carried out his daily professional chores. The tremendous advances and number of publications on cardiology in the few years since the second edition of this book have been almost countless. In the preface the author has listed most of the new developments in this field, which are too numerous to set down in a brief book review. It would be idle to go into details about the contents and quality of this book. All who are interested in diseases of the heart should possess it.

T. TAYLOE PERRY, M.D.

Ocular Pharmacology. WILLIAM H. HAVENER, B.A., M.D., M.S. (Ophth.). Price, $21.75. Pp. 456, with 198 illustrations. St. Louis: Mosby, 1966.

One who has read the popular current American literature in ophthalmology for the past 10 years will find nothing new in this book. He will find most of the useful articles pertaining to ocular pharmacology well summarized and presented in an orderly manner. That was the author's expressed purpose, and the job is well done.

Acknowledgment of sources is conscientiously complete.

The author did not intend to make a handy guide to clinical treatment, and this book will not serve in that capacity.

Excellent, good and fair articles are included with an uncritical impartiality. Some readers might have appreciated some expert evaluation of many of the studies which are reported.

The index is adequate. The paper, printing, and binding are excellent.

The book will be of particular value to newcomers in ophthalmology and to those who wish to review this particular subject.

ROBERT P. KLING, M.D.

The Pediatrician's Ophthalmology. A collaborative effort of several authors. Edited by SUMNER D. LIEBMAN, M.D., AND SYDNEY S. GELLIS, M.D. Price, $19.50. Pp. 352, with 120 text illustrations and 7 color plates. St. Louis: Mosby, 1966.

This text and reference book represents the collaborative efforts of 25 contributors, the majority of whom are ophthalmologists. It is jointly edited by Dr. Leibman, an ophthalmologist associated with Harvard Medical School, and Dr. Gellis, Professor and Chairman of the Department of Pediatrics of Tufts University School of Medicine.

The subject matter has been specifically written for pediatricians and physicians in general practice, with the stated intention of presenting "material which pediatricians feel they need most" regarding the eye and its disorders. The technical terminology inherent and peculiar to ophthalmology, but so often unfamiliar in general medical circles, has been generally avoided, and the inclusion of a glossary of ophthalmic terms is additionally helpful.

Several chapters are of particular clinical value to any physician examining and treating children. The section on Ocular Manifestations of Pediatric Systemic Diseases is most thorough in its scope and extensive bibliography. The chapter on External Diseases includes great detail on all aspects of corneal and con-

(*Continued on pages 44*)

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Book Reviews

(*Continued from page 42*)

junctival disease and is illustrated by a number of exceptionally fine color photographs.

The section on Genetic Applications to Pediatric Ophthalmology consists of an excellent review of basic genetics plus a 12-page chart listing nearly 120 inherited conditions that manifest ocular pathology. Specific notations are made of the mode of inheritance, ocular manifestations, and principal nonocular manifestations. This is an invaluable reference even for ophthalmologists.

Dr. Frank D. Costenbader's section on Strabismus is based on many years of experience with disorders of ocular motility and is presented in clear and understandable terms for those unfamiliar with this complex subject. There is repeated emphasis on the importance of early recognition and early treatment of children with ocular muscle imbalance.

The chapter on Methods of Examination by Dr. Marshall M. Parks is all-inclusive in his description of numerous techniques available to, and utilized by ophthalmologists in evaluating ocular deformities, injuries, inflammation, and visual disorders. For those giving screening type visual examinations in the office, this discussion should aid them considerably in the recognition of structural disorders and aberrations of visual function.

One chapter is devoted to the perplexing problem of Specific Reading Disability with a realistic consideration of its diverse etiology and the present status of treatment.

The chapter on Developmental and Acquired Cataracts comments in detail on the morphologic characteristics of these lens opacities; however, it has completely neglected to mention the significant technical advances in the surgical treatment of congenital cataracts which have evolved over the past 5 years.

It also seems to this reviewer that the section on Refraction would be more meaningful and understandable if illustrated with diagrams and charts.

Because the first several years of life are critical in developing good binocular vision and stable ocular alignment, a great responsibility lies with those physicians having intimate contact with infants and children during this time. This book will serve those physicians well in developing a proficiency in the early recognition of ocular abnormalities and should stimulate a greater understanding of those eye disorders peculiar to children.

JOHN F. O'NEILL, M.D.

Early Management of Acute Trauma. Edited by ALAN M. NAHUM, M.D. Price, $21.00. Pp. 336, with 271 figures. St. Louis: Mosby, 1966.

This book does not identify or define the relative meaning of "early." Obviously, the term "early" means 1 to 8 minutes in cardiac arrest and may mean 1 to 7 days in fracture patients. Other sections deal at some length with the management of late complications. This was not always related in the text to appropriate early treatment. For example, the discussion of myositis ossificans in athletes fails to indicate what measures reduce the incidence of this condition, while describing excision of the lesion 1 year later.

In concept, early emergency room treatment of the injured patient is a worthy topic for multiple authorship. However, current textbooks on surgery combine most of the material presented in this book in a more succinct fashion, and allow the reader to include late management in greater detail. Closer editing would have prevented repetitive references to general principles, such as management of shock, respiratory obstruction, visceral injuries as well as frequent philosophical observations on the role of physician training, adequate lighting, good quarters and abundant auxiliary personnel.

Although the subject matter is well selected, many sections offer classic textbook presentations. In the section on shock, the proven methods of management are compared to recent controversial methods in a fashion to cast doubt on which new method is appropriate for a particular type of shock. For these, and similar problems of presentation, the book fails to live up to its title.

ROBERT G. KINDRED, M.D.

Symposium on Surgery of the Ocular Adnexa. Transactions of the New Orleans Academy of Ophthalmology. CONTRIBUTORS: Arthur Gerard DeVoe, M.D., Sidney A. Fox, M.D., Howard Naquin, M.D., T. E. Sanders, M.D., Byron Smith, M.D., Everett R. Veirs, M.D., and Joseph A. C. Wadsworth, M.D. Price, $16.00. Pp. 245, illustrated. St. Louis: Mosby, 1966.

The title of this volume to some extent belies the content; although the emphasis is definitely on techniques of surgical procedures about the eye, considerable time is devoted to diagnostic procedures, nonsurgical treatment, and pathology. At least 4 of the 18 chapters are devoted almost entirely to nonsurgical subjects.

Byron Smith and Sidney Fox each contribute several chapters on plastic procedures, and although this material is quite readable and authoritative, it contains very little, if any, information that has not previously been published by these gentlemen.

Some of the most valuable material in this book is contained in the round-table discussions at the end of the volume. The personal preferences of the authors on diagnostic and therapeutic procedures in many specific problems are revealed, and several controversial subjects in management are debated.

This book is recommended not as a basic text on surgery of the ocular adnexa but as an exposition of the current thinking of several ophthalmologists having wide experience in this field. It should prove of value in dealing with certain specific cases encountered by the practicing ophthalmologist and as a general review of the field.

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Reference: 1. Roberts, C. E., Jr.; Perry, D. M.; Kuharic, H. A., and Kirby, W. M. M.: A. M. A. Arch. Int. Med. 107:204 (Feb.) 1961.

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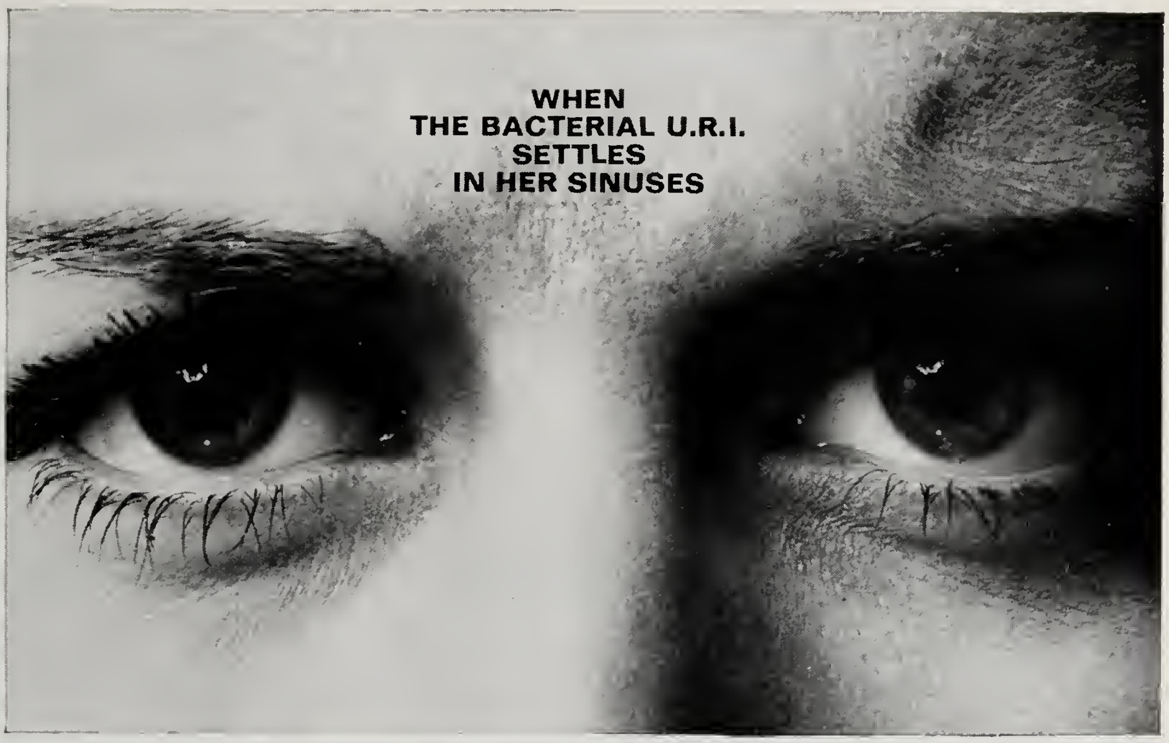

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January 22–23: National Congress on the Socio-Economics of Health Care. Palmer House, Chicago. Address: Division of Socio-Economic Activities, American Medical Association, 535 North Dearborn Street, Chicago, Ill. 60610.

February 9–15: Congress on Medical Education. Palmer House, Chicago. Address: Dr. Walter S. Wiggins, American Medical Association, 535 North Dearborn Street, Chicago, Ill. 60610.

February 15–19: American College of Cardiology. Washington Hilton Hotel, Washington. Address: Mr. William D. Nelligan, Executive Director, 9650 Rockville Pike, Washington, D. C. 20014.

March 5–9: International Anesthesia Research Society (41st Congress). Americana Hotel, Bal Harbour, Fla. Address: Dr. B. B. Sankey, Executive Secretary, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

March 10–12: American Association of Pathologists and Bacteriologists. Sheraton-Park Hotel, Washington. Address: Dr. J. Lowell Orbison, University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. 14620.

March 12–15: International Academy of Pathology. Sheraton Park Hotel, Washington. Address: Dr. F. K. Mostofi, Secretary-Treasurer, Armed Forces Institute of Pathology, Washington, D. C. 20305.

March 12–15: 35th Annual Postgraduate Clinic of the District of Columbia Dental Society. Shoreham Hotel, Washington. Address: Ashur G. Chavoor, D.D.S., General Chairman, D. C. Dental Society, 1835 Eye Street, N.W., Washington, D. C. 20006.

March 20–23: American Orthopsychiatric Association (44th Annual Meeting). Washington Hilton Hotel, Washington. Address: Dr. William Stark, Co-chairman of Local Arrangements, 5415 Connecticut Avenue, N.W., Washington, D. C. 20015.

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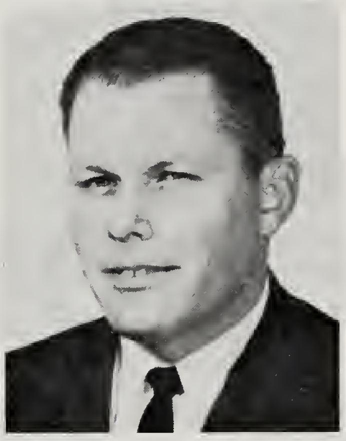

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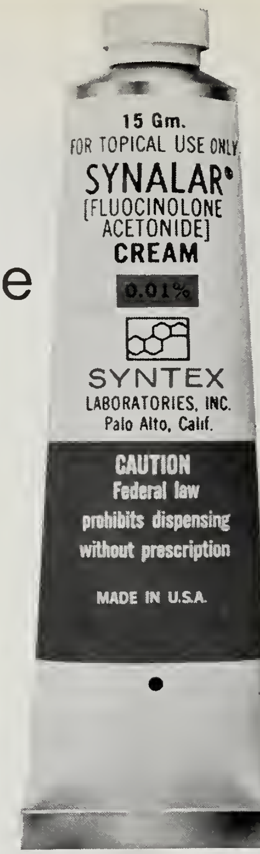

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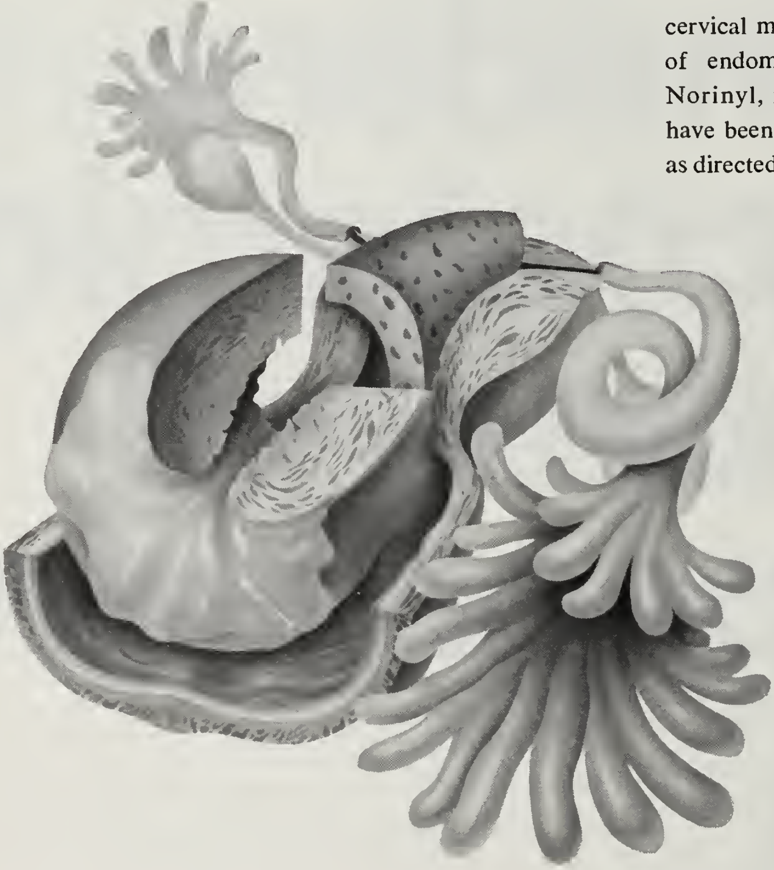

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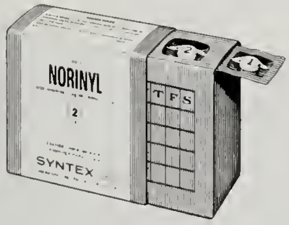

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Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

References: 1. Council on Drugs JAMA 187 664 (Feb 29) 1964 **2.** Bryans, F. E.: Canad Med Ass J 92 287 (Feb. 6) 1965. **3.** Goldzieher, J. W · Med Clin N Amer 48:529 (Mar.) 1964 **4.** Cohen, M. R.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif , July 15, 1965. Reported in Med Sci 16·26 (Nov.) 1965. **5.** Hammond, D. O Ibid. **6.** Rice-Wray, E., Goldzieher, J. W., and Aranda-Rosell, A · Fertil Steril 14:402 (Jul.-Aug.) 1963. **7.** Goldzieher, J. W . Moses, L E., and Ellis, L. T : JAMA 180:359 (May 5) 1962. **8.** Kempers, R. D.: GP 29·88 (Jan.) 1964 **9** Tyler, E. T.: JAMA 187:562 (Feb. 22) 1964. **10.** Rudel, H. W , Martinez-Manautou, J., and Maqueo-Topete, M · Fertil Steril 16:158 (Mar.-Apr.) 1965. **11.** Flowers, C. E., Jr.: N Carolina Med J 25·139 (Apr.) 1964 **12.** Goldzieher, J. W · Appl Ther 6:503 (June) 1964 **13.** The Control of Fertility. Report adopted by the Committee on Human Reproduction of the American Medical Association. JAMA 194:462 (Oct. 25) 1965. **14.** Flowers, C. E., Jr.: JAMA 188:1115 (June 29) 1964. **15.** Merritt, R. I.· Appl Ther 6:427 (May) 1964. **16.** Newland, D. O.: Paper presented at Symposium on Low-Dosage Oral Contraception, Palo Alto, Calif., July 15, 1965. Reported in Med Sci 16:26 (Nov.) 1965.

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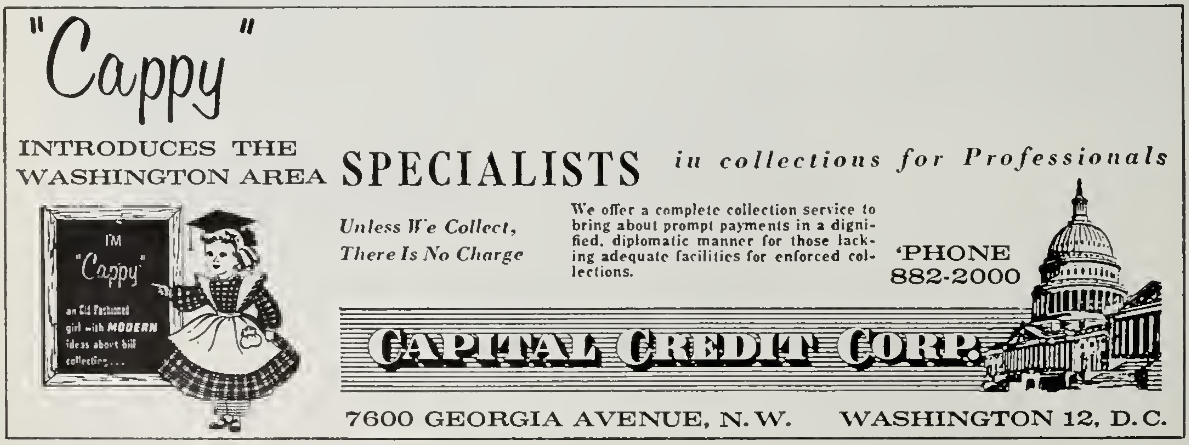
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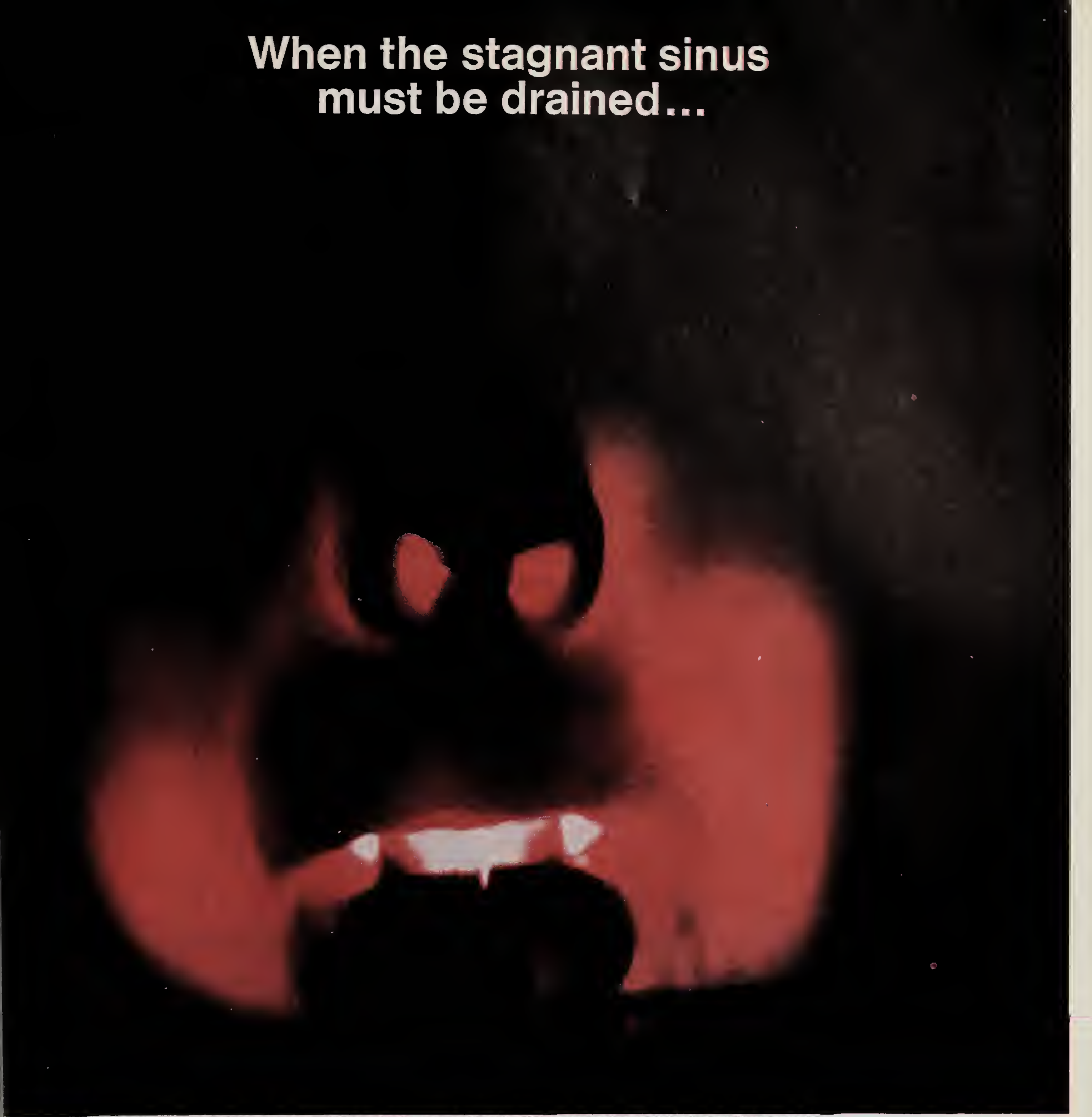

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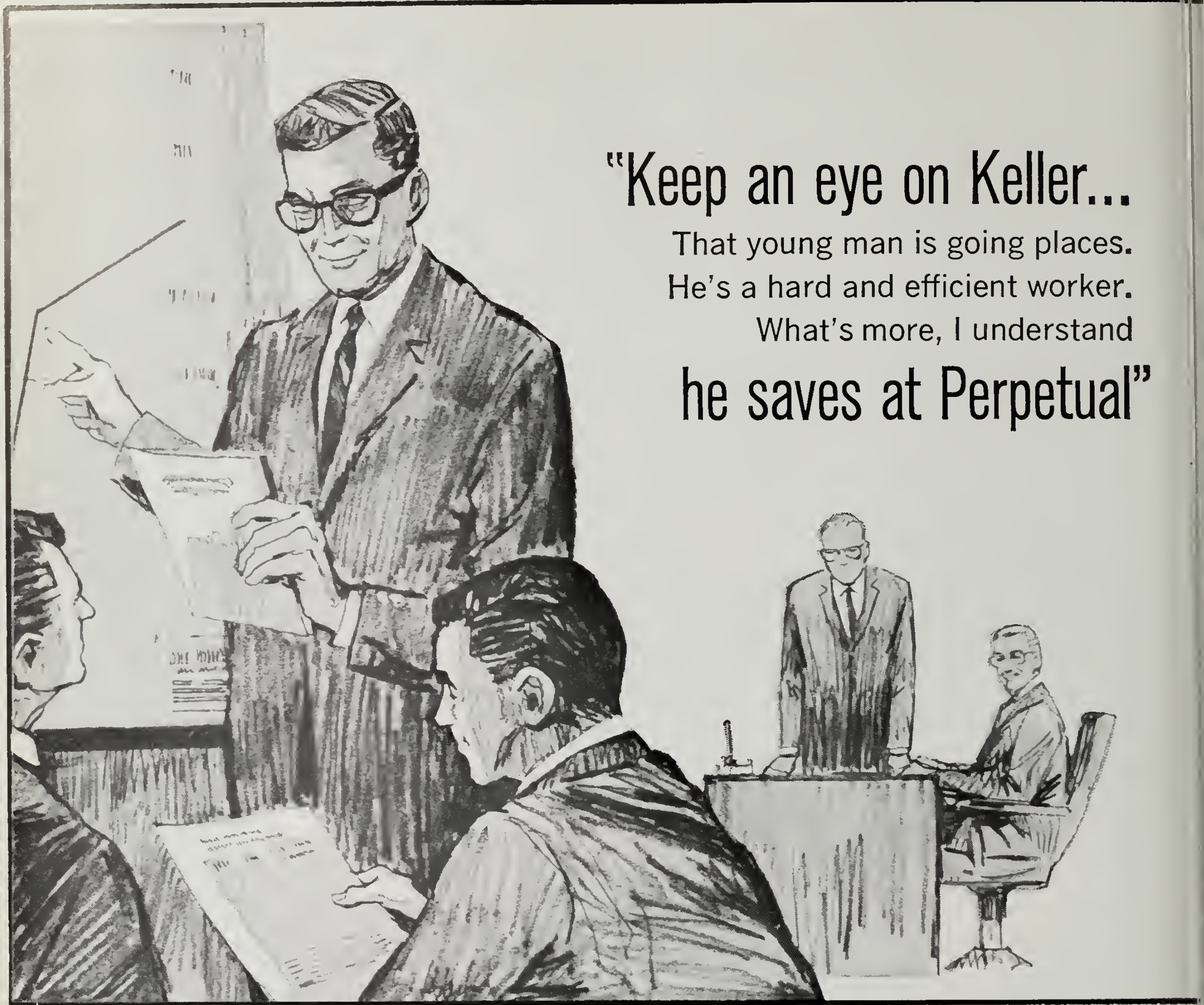
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T–text

SQUIBB NOTES ON THERAPY

MOLECULAR REMODELING—

laboratory exercise or clinical necessity?

More than twenty-five years have passed since the discovery of the diuretic activity of sulfanilamide started pharmacologists on a succession of molecular remodelings to find the ideal diuretic.

Diuresis—a sought-after clinical effect from an unwanted side effect

It started in 1937 when a clinician reported that the administration of a sulfonamide was sometimes accompanied by an unexplainable side effect—metabolic acidosis.[1] Three years later the side effect was explained. The sulfonamide radical of sulfanilamide inhibited carbonic anhydrase,[2] the enzyme responsible for converting carbon dioxide and water to hydrogen ions and bicarbonate ions.

Later, other investigators showed by dog experiments that metabolic acidosis probably resulted when the inhibition of carbonic anhydrase upset the exchange of hydrogen and sodium ions, causing increased excretion of sodium as the bicarbonate.[3]

It was twelve long years after the first report of the unexplainable side effect (metabolic acidosis) that it was finally shown that large doses of sulfanilamide administered to edematous patients were indeed capable of promoting diuresis.[4] However, the possibility of toxic effects from its prolonged use and its relatively weak diuretic action made it impractical for clinical use as a diuretic.[5]

Because the inhibition of carbonic anhydrase seemed to be the key to effective diuresis, investigators began to look for more potent enzyme inhibitors—in the hopes that they would be more effective diuretics.

The most important of these early compounds, acetazolamide, enjoyed several years of fairly wide clinical use.

Its carbonic anhydrase inhibitory activity was several hundred times greater than that of sulfanilamide.[6] The increase in inhibitory activity, however, increased not only the excretion of sodium and bicarbonate ions, but also the excretion of potassium.[7] And, like its predecessor, acetazolamide precipitated mild acidosis. Its prolonged use could result in hypokalemic acidosis.[7]

The 'thiazides'—an answer to the metabolic acidosis caused by carbonic anhydrase inhibition

Despite the fact that the sulfonamide group appeared to be responsible for carbonic anhydrase inhibition which in turn appeared to be responsible for diuresis, investigators began to synthesize compounds with structural alterations to the sulfonamide group.

The first major breakthrough came with the synthesis of chlorothiazide. Altering the sulfonamide group did indeed alter the ability of chlorothiazide to inhibit carbonic anhydrase—it was only 1/10th as potent as acetazolamide in inhibiting the enzyme.[8] Despite the drop in inhibitory potency, however, chlorothiazide proved to be an effective diuretic—an observation that led to the conclusion that its diuretic action was due to some mechanism other than its action on carbonic anhydrase.[9,10]

For effective diuresis, chlorothiazide was administered in daily dosages ranging from 250 to 2000 mg.[11] It increased the excretion of sodium and chloride; and, to a lesser extent, potassium and bicarbonate.[11] The excretion of potassium appeared to be maximal at higher dose levels at which, theoretically, the carbonic anhydrase inhibitory effect is more active.[11] Its prolonged use, therefore, could sometimes result in metabolic hypokalemic, hypochloremic alkalosis.[7]

Naturetin—effective diuresis with more favorable electrolyte balance

Other thiazides followed—with improvements being aimed at two particular areas: 1. attempts to increase diuretic action in relation to the milligram potency of the drug, and 2. attempts at a more favorable sodium/potassium ratio in the urine, i.e., to decrease the excretion of potassium while maintaining the excretion of sodium.[12]

One of these, Naturetin, Squibb Bendroflumethiazide, has made advances on both these points. "By adding a 3-benzyl radical to hydroflumethiazide a rather dramatic reduction in dose range is accomplished. With this drug, effective sodium excretion is obtained with doses between 2.5 and 10 mg., which is a 200 to 1 ratio as compared to chlorothiazide..."[13]

Moreover, due probably to its virtual lack of carbonic anhydrase inhibition, Naturetin (bendroflumethiazide) has been shown to cause less potassium and bicarbonate loss and less alteration in urinary pH than either chlorothiazide or hydrochlorothiazide.

Naturetin is outstandingly effective not only in establishing, but also in maintaining, excretion of retained fluid in edematous patients. And its duration of action is sufficiently prolonged to allow a single daily administration in most patients. Naturetin is also an effective antihypertensive agent.

Contraindications: Severe renal impairment; previous hypersensitivity.

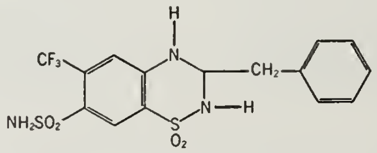
Warning: Ulcerative small bowel lesions have occurred with potassium-containing thiazide preparations or with enteric-coated potassium salts supplementally. Stop medication if abdominal pain, distension, nausea, vomiting, or G.I. bleeding occur.

Precautions: The dosage of ganglionic blocking agents, veratrum, or hydralazine when used concomitantly must be reduced by at least 50% to avoid orthostatic hypotension. Electrolyte disturbances are possible in cirrhotic or digitalized patients.

Side Effects: Bendroflumethiazide may cause increases in serum uric acid, unmask diabetes, increase glycemia and glycosuria in diabetic patients and may cause hypochloremic alkalosis, hypokalemia; cramps, pruritus, paresthesias, and rashes may occur.

Supplied: Naturetin (Squibb Bendroflumethiazide) 5 mg. and 2.5 mg. tablets. Also available Naturetin c̄ K [Squibb Bendroflumethiazide (5 or 2.5 mg.) with Potassium Chloride (500 mg.)]. For full information, see Product Brief.

References: 1. Southworth, H.: Proc. Soc. Exper. Biol. & Med. *36*:58, 1937. **2.** Mann, T. and Keilin, D.: Nature *146*:164, 1940. **3.** Pitts, R. F., and Alexander, R. S.: Am. J. Physiol. *144*:239, 1945. **4.** Schwartz, W. B.: New England J. Med. *240*:173, 1949. **5.** Friedberg, C. K., in Moyer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia, W. B. Saunders Co., 1960, p. 259. **6.** Cumming, J. R.; Tabachnick, E., and Seelig, M., in Moyer, J. H., and Fuchs, M.: op. cit., p. 254. **7.** Werko, L., in Moyer, J. H., and Fuchs, M.: op. cit., p. 188. **8.** Beyer, K. H., Jr., in Moyer, J. H., and Fuchs, M.: op. cit., p. 274. **9.** Maren, T. H., and Wiley, C. E.: J. Pharmacol. & Exper. Therap. *143*:230, 1964. **10.** Earley, L. E., and Orloff, J.: Ann. Rev. Med. *15*:149, 1964. **11.** Fuchs, M., and Mallin, S. R., in Moyer, J. H., and Fuchs, M.: op. cit., p. 276. **12.** Ford, R. V., in Moyer, J. H., and Fuchs, M.: op. cit., p. 290. **13.** cited in Fuchs, M., and Mallin, S. R. (ref. 11): op. cit., p. 283.



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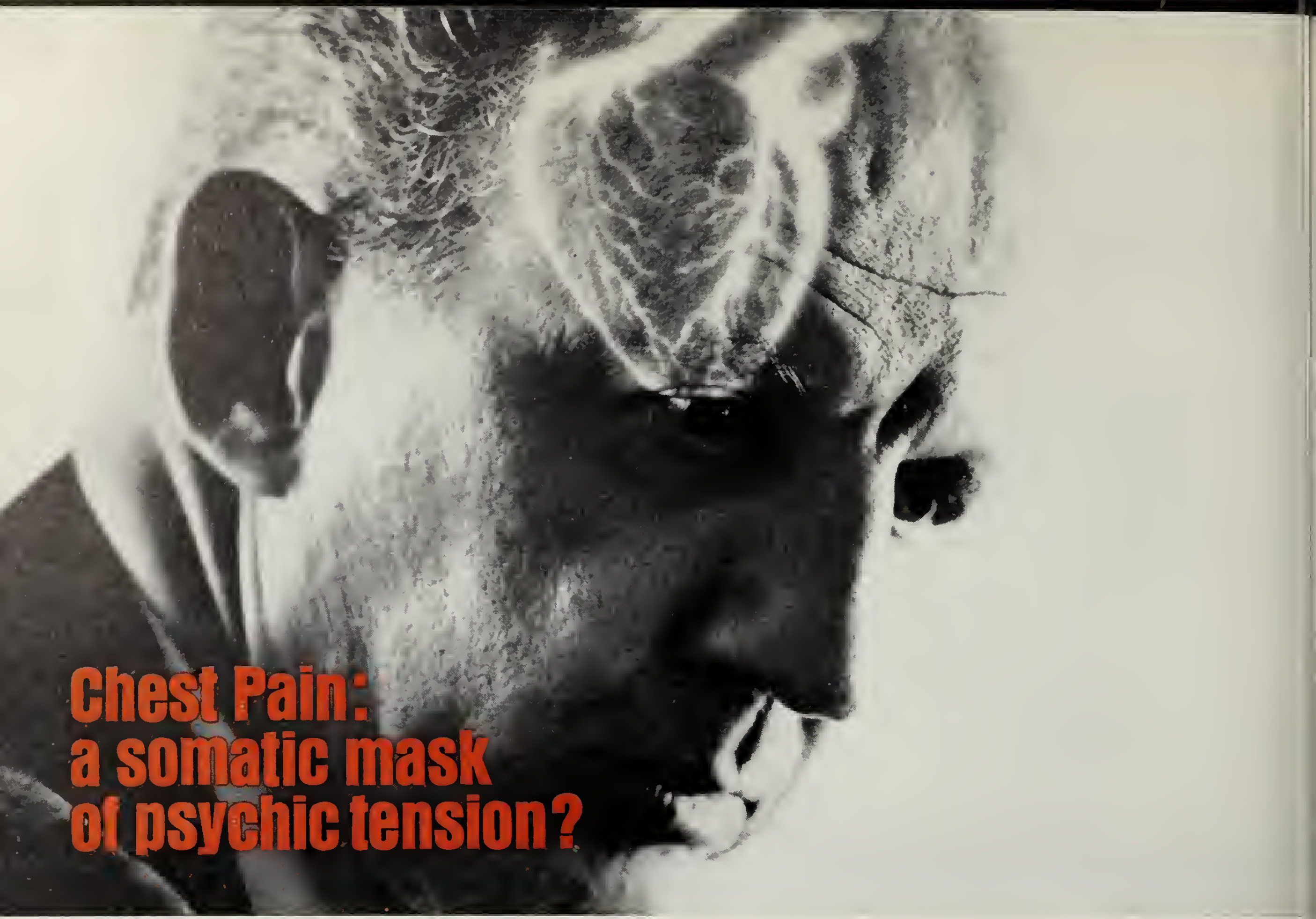

"Heart symptoms"—chest pain, tachycardia, arrhythmia—invariably alarm and preoccupy the patient, though they may be completely without organic basis. Such symptoms often are somatic masks of psychic tension, arising from constant encounters with stressful situations.

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Valium (diazepam) is generally well tolerated, and usually does not impair mental acuity or ability to function. If side effects such as ataxia and drowsiness occur, they usually disappear with dosage adjustment.

Contraindications: Infants, patients with history of convulsive disorders or glaucoma.

Warning: Not of value in the treatment of psychotic patients, and should not be employed in lieu of appropriate treatment.

Precautions: Limit dosage to smallest effective amount in elderly patients (not more than 1 mg, one or two times daily) to preclude ataxia or oversedation. Advise patients against possibly hazardous procedures until correct maintenance dosage is established; driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. Warn patients of possible combined effects with alcohol. Safe use in pregnancy not established. Observe usual precautions in impaired renal or hepatic function and in patients who may be suicidal; periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.

Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances and hallucinations) and changes in EEG patterns. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.

Dosage — Adults: Mild to moderate psychoneurotic reactions, 2 to 5 mg b.i.d. or t.i.d.; severe psychoneurotic reactions, 5 to 10 mg t.i.d. or q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hrs, then 5 mg t.i.d. or q.i.d. as needed; muscle spasm with cerebral palsy or athetosis, 2 to 10 mg t.i.d. or q.i.d. Geriatric patients: 1 or 2 mg/day initially, increase gradually as needed.

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